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(54) Novel derivatives of benzimidazoles active as anti-ulcer agents.

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EP-A- 174 717
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EP-A- 0 172 631
EP-A- 0 178 413
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EP 0 266 326 B1

Description

Field of the invention

The object of the present invention is to provide novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and are thus useful as anti-ulcer agents. The compounds also provide gastrointestinal cytoprotective effects and can be used in the prevention of peptic ulcer. The new compounds are more short acting than compounds prior known.

The present invention relates to the use of the compounds of the invention or therapeutically acceptable salts thereof, for inhibiting gastric acid secretion as well as providing gastrointestinal cytoprotective effects in mammals and man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals and man, including e.g. gastritis, gastric ulcer, and duodenal ulcer. Furthermore, the compounds may be used for prevention and treatment of other gastrointestinal disorders, where cytoprotective and/or gastric antisecretory effect is desirable e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive ethanol consumption. The invention also relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compounds.

Prior art

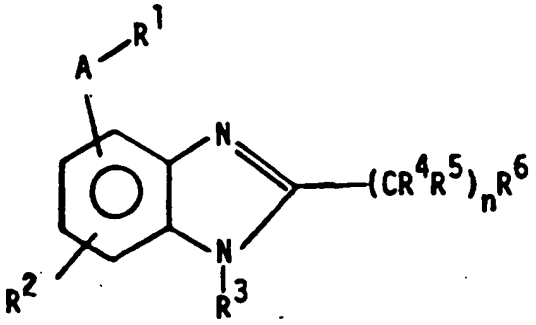
Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the British patent specifications 1 500 043 and 1 525 958, in the US patent 4 182 766, in the European patent specification 0 005 129 and in the Belgian patent specification 890 024. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory disease are disclosed in the European patent application with publication no. 0 045 200. The compounds disclaimed in the definition of the compounds with the general formula I are described as intermediates in European patent application 178 413. The last mentioned European patent application describes also other similar compounds for use in the treatment of inflammatory conditions, e.g. rheumatism and arthritis.

DE-A-25 05 913, GB-A-21 34 523, EP-A-0125 756, EP-A-0174 717, Nature 290,159(1981) and TIPS 5, 262(1984) describe benzimidazoles without the three structural elements which according to Scandinavian Journal of Gastroenterology, Supplement No 108,(1985) pages 15-22 were considered to be needed for an gastric antisecretory effect, namely

1) substituted pyridine ring
2) substituted benzimidazole ring, and
3) the chain between these two, which must be $-CH_2S-$ or $-CH_2SO-$.

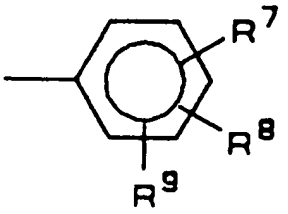
The invention

It has been found that compounds of the general formula I



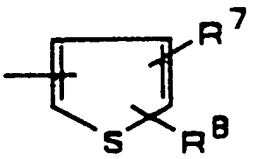
I

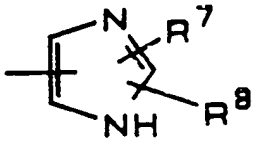
or a pharmaceutically acceptable salt or solvate thereof, in which
R^1 represents a substituted or unsubstituted aryl group of the formula II'

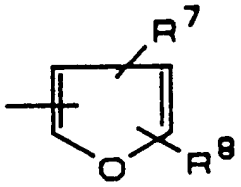


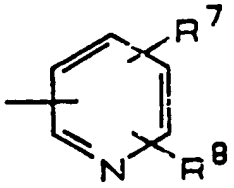
II'

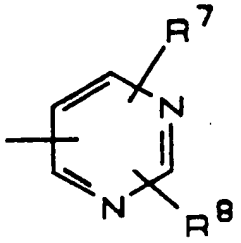
in which each of R^7, R^8, R^9 independently represents hydrogen, an alkyl having up to 6 carbon atoms, an alkoxy having up to 6 carbon atoms, halogen, preferably chloro or fluoro, or a heterocyclic aryl group of one of the following formulas











in which R^7 and R^8 have the meanings given above;
or a cycloalkyl group with 3-8 carbon atoms in the unsubstituted cyclic group; or an adamantyl group;
R^2 represents hydrogen, an alkyl containing up to 6 carbon atoms, an alkoxy containing up to 6 carbon atoms, or halogen;
R^3 represents hydrogen, an alkyl containing up to 6 carbon atoms, a phenylalkyl with 1-4 carbon atoms in the alkyl group or a cycloalkyl-alkyl group with 3-8 carbon atoms in the cyclic group and 1-4 carbon atoms in the alkyl group;
n is an integer 0-6;
R^4 represents hydrogen or an alkyl containing up to 6 carbon atoms;
R^5 represents hydrogen or an alkyl containing up to 6 carbon atoms;
R^6 represents hydrogen, an alkyl containing up to 6 carbon atoms, a substituted or unsubstituted aryl group as defined above for R1 or when n is 1-6 a hydroxyl group or when n is 0 an amino, an alkylamino or a dialkylamino group with 1-4 carbon atoms in the alkyl groups;
A represents an alkylene up to 6 carbon atoms, optionally connected to, or interrupted by an optionally substituted hetero atom selected from O, S, and NR, wherein R is hydrogen, an alkyl containing up to 6 carbon atoms, a phenylalkyl with 1-4 carbon atoms in the alkyl group or a cycloalkyl-alkyl group with 3-8 carbon atoms in the cyclic group and 1-4 carbon atoms in the alkyl group; or an alkenylene with up to 6 carbon atoms

with the provisos that when

a) n is 0 and R^2, R^3 and R^6 are all hydrogen, then the group A-R^1 is not 7-benzylamino or 7-(4'-methoxy)-benzylamino; and when

b) n is 1 and R^3, R^4 and R^5 are all hydrogen, R^2 is 4-methyl, R^6 is ethyl, phenyl, benzyl, or (4'-methoxy)-phenyl then the group A-R^1 is not 7-benzyloxy; and when

c) n is 0, R^2 is 4-methyl, R^3 is hydrogen and R^6 is phenyl, then the group A-R^1 is not 7-benzyloxy.

A representing an alkylene, optionally connected to, or interrupted by an optionally substituted hetero atom has preferably up to 6 carbon atoms.

According to the invention,A may represent any of the following

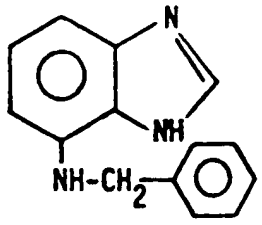
i) $-(CH_2)_m-$, wherein m is 1-6

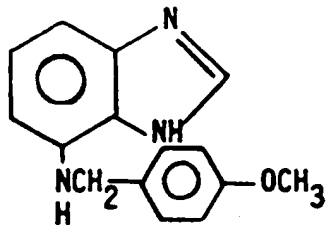
ii) $-X-(CH_2)_m-$, wherein m is as defined above and X is O, S or NR, wherein R is as defined above

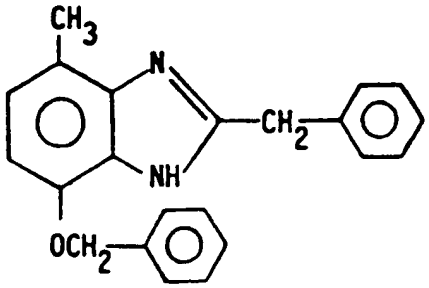
iii) $-(CH_2)_x-X(CH_2)_y-$, wherein x and y are integers with a sum of 1-6 and X is as defined above or

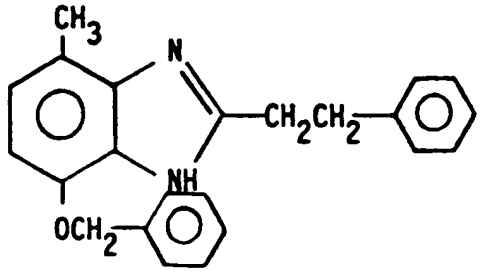
iv) alkenylene with up to 2-6 carbon atoms. Examples of alkenylene groups are -CH=CH- and $-CH_2-CH=CH-$.

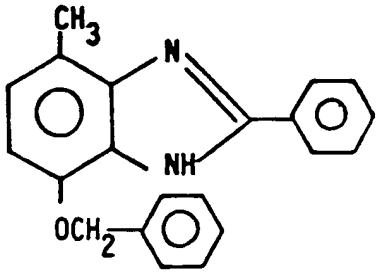
The following compounds are excluded from the scope of this application.

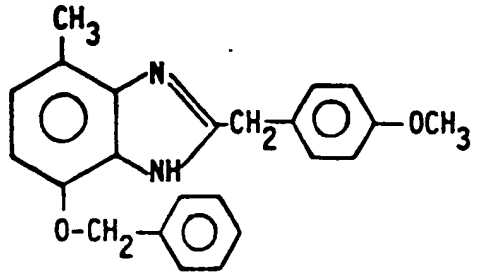


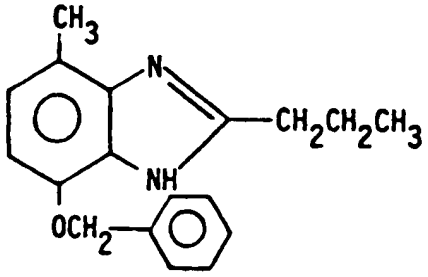












Both the pure enantiomers, racemic mixtures and unequal mixtures of the two enantiomers are within the scope of the present invention. It should be understood that all the diastereomeric forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

Especially preferred groups of R^1 according to the invention are

R^1 representing phenyl, 2'-F-phenyl, 3'-F-phenyl, 4'-F-phenyl, 4'-Cl-phenyl, 2',4'-di-F-phenyl, 2',4'-di-Cl-phenyl and thienyl-2.

Especially preferred groups of R^2, R^4 and R^5 are hydrogen.

Especially preferred groups of R^3 are hydrogen or methyl.

Especially preferred groups of R^6 are hydrogen, hydroxy or phenyl.

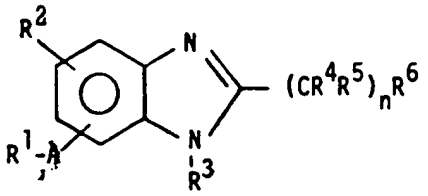
Especially preferred groups of A are 4-OCH_2, 5-OCH_2, 7-OCH_2, 4-$NHCH_2$ and 4-OCH_2CH_2.

An especially preferred compound according to the invention is 4-benzyloxy-2-methylbenzimidazole.

Illustrative examples of compounds included in the scope of the invention are given in the examples and in the following Table 1.

Table 1

Illustrative examples of compounds included in the scope of the invention



R^3	$(CR^4R^5)_nR^6$	R^2	$A\text{-}R^1$
H	H	H	4-OCH_2-Ph
H	CH_3	H	4-OCH_2-Ph
H	CH_2CH_3	H	4-OCH_2-Ph
CH_3	CH_3	H	4-OCH_2-Ph
CH_3	CH_3	H	7-OCH_2-Ph
H	CH_3	H	5-OCH_2-Ph
H	CH_3	H	4-$NHCH_2$-Ph
H	CH_3	H	4-OCH_2CH_2-Ph
H	$CH(CH_3)_2$	H	4-OCH_2-Ph
H	CH_2-Ph	H	4-OCH_2-Ph
CH_2CH_3	CH_3	H	4-OCH_2-Ph
$CH(CH_3)_2$	CH_3	H	7-CH_2CH_2-Ph

cont.

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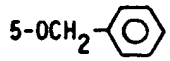
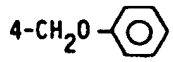
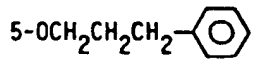
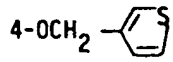
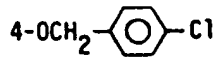
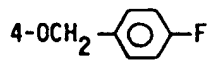
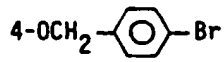
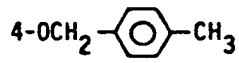
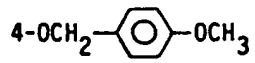
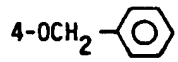
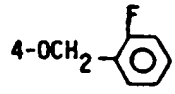
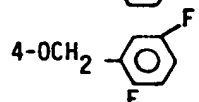
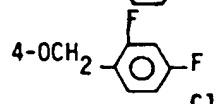
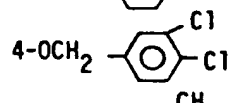
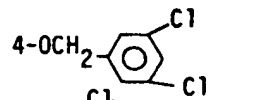
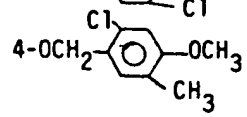
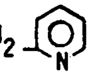
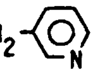
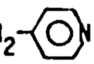
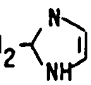
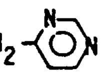
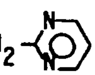
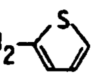
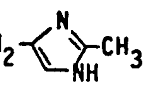
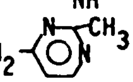
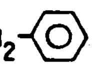
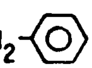
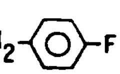
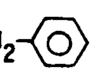
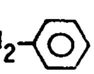
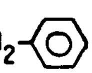
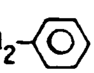
R^3	$(CR^4R^5)_nR^6$	R^2	$A\text{-}R^1$
H	H	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_2OH	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	
H	CH_3	H	

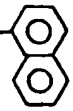
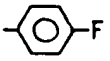
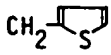
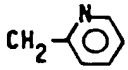
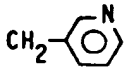
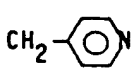
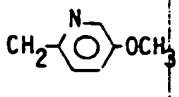
cont.

cont.

R^3	$(CR^4R^5)_nR^6$	R^2	$A\text{-}R^1$
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H	CH_3	H	4-OCH_2 
H		H	4-OCH_2 
H	CH_3	4-CH_3	7-OCH_2 
H	CH_3	4-Cl	7-OCH_2 
H	CH_3	5-OCH_3	7-OCH_2 
H	CH_2CH_3	6-Br	7-OCH_2 
CH_3	CH_3	4-CH_3	7-OCH_2 
CH_3	CH_3	7-CH_3	4-OCH_2 

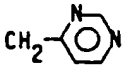
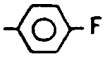
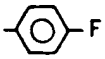
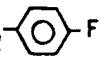
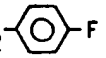
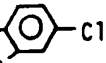
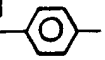
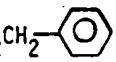
cont.

cont.

R^3	$(CR^4R^5)_nR^6$	R^2	A-R^1
H	CH_3	H	4-OCH_2- 
H	CH_3	H	4-$N(CH_3)$-CH_2- 
H	CH_3	H	4-SCH_2- 
H	CH_3	H	4-CH_2OCH_2- 
H	CH_3	H	4-CH_2- 
H	CH_3	H	4-CH=CH- 
CH_3	CH_3	H	4-$CH_2CH_2CH_2$- 
H	$CH(CH_3)_2$	H	4-CH=$CHCH_2$- 
H	$C(CH_3)_3$	4-Cl	7-OCH_2- 
H	CH_2- 	7-CH_3	4-OCH_2- 
H	CH_2- 	H	4-OCH_2- 
H	CH_2- 	4-Br	7-OCH_2- 
H	CH_2- 	7-OCH_3	4-OCH_2- 
H	CH_2- 	H	4-OCH_2- 
H	CH_3	H	4-CH_2CH_2S- 
H	CH_3	H	4-$NHCH_2CH_2$- 
H		H	4-OCH_2- 

cont.

cont.

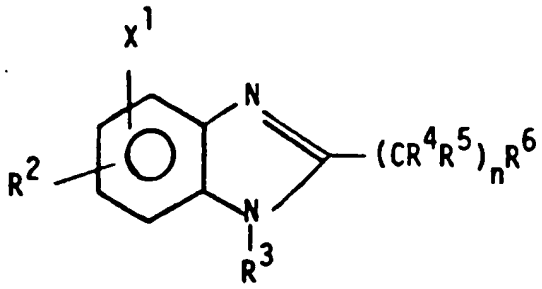
R^3	$(CR^4R^5)_nR^6$	R^2	A-R^1
H		H	4-OCH_2- 
H	CH_2- 	H	4-OCH_2- 
H	$CH(CH_3)$- 	H	4-OCH_2- 
H	CH_3	4-CH_3	7-OCH_2- 
H	CH_3	7-CH_3	4-OCH_2- 
H	CH_3	H	5-OCH_2- 
H	CH_3	5-Cl	6-OCH_2- 
H	NH_2	H	4-OCH_2- 
H	CH_3	H	4-OCH_2- 
H	CH_3	H	4-$NHCH_2$- 
H	CH_3	H	-4-$N(CH_2C_6H_5)CH_2$- 
CH_2CH_2-	CH_3	H	4-OCH_2- 
CH_2CH_2-	CH_3	H	7-OCH_2- 
H	$N(CH_3)_2$	H	4-OCH_2- 
H	CH_3	H	4-OCH_2- 
H	$NH(CH_3)$	H	4-OCH_2- 
H	CH_3	H	5-OCH_2CH_2- 
CH_2-	CH_3	H	4-OCH_2- 
H	CH_3	H	4-OCH_2- 

Preparation

The present invention also provides processes for the manufacture of the compounds with the general formula I.

The compounds are prepared in the following way.

A. A compound of the general formula II



II

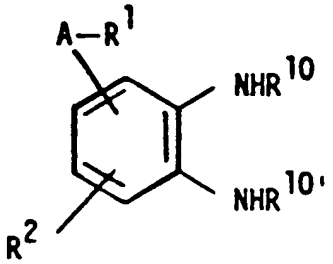
wherein R^2, R^3, R^4, R^5 and R^6 are as defined above is reacted with a compound of the formula III

$R^1(CH_2)_mX^2$ III

wherein R^1 is as defined above, X^1 is -OH, -SH, or -NHR and X^2 is a leaving group, such as a halide, tosyloxy or mesyloxy; and m is an integer 1-6 whereby a compound of the general formula I, wherein R^1, R^2, R^3, R^4, R^5, R^6 and n are as defined above and A is $-O(CH_2)_m$, $-S(CH_2)_m$ or $-NR(CH_2)_m$ is obtained.

It is convenient to conduct this reaction in the presence of a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide; a sodium alcoholate, such as sodium methoxide and sodium ethoxide; and alkali metal hydride, such as sodium hydride and potassium hydride; an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine. The solvent used for the reaction is preferably alcohol, e.g. methanol or ethanol, or another polar solvent such as dimethylformamide. The reaction temperature ranges usually from about 0 °C to about the boiling point of the solvent used, more preferably from about 20 °C to about 80 °C. The reaction time ranges from about 0.2 to about 24 hours, more preferably from about 0.5 to about 2 hours.

B. A compound of the general formula IV

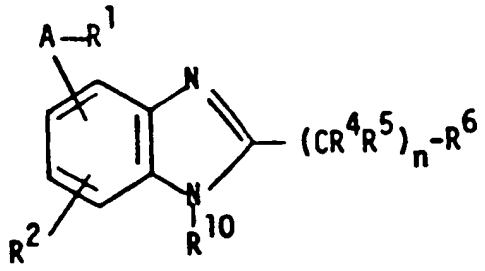


IV

wherein R^1 and R^2 are as defined above, R^{10} and $R^{10'}$ are the same or different and each is hydrogen, a lower alkyl group having up to 6 carbon atoms or a group or atom convertible to a lower alkyl group with the proviso that when one of R^{10} and $R^{10'}$ is a lower alkyl group or a group or atom convertible to a lower alkyl group the other of R^{10} and $R^{10'}$ is hydrogen
is reacted with a compound of the general formula V

$R^6(CR^4R^5)_nCOR^{11}$ V

wherein R^4, R^5, R^6 and n are as defined above and R^{11} is a leaving group such as halide, hydroxy, alkoxy, acyloxy or alkoxycarbonyloxy or hydrogen, whereby a compound of the general formula IV

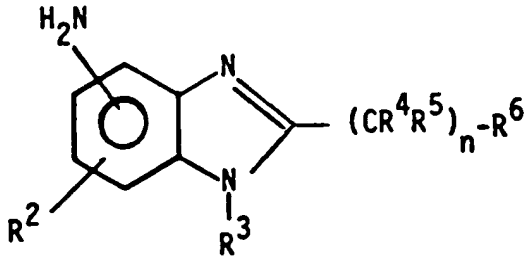


VI

is formed and, if required, a nitrogen atom of the benzimidazole nucleus is alkylated and, if required, protecting groups are removed, to form a compound of the general formula I, and if required, a salt or solvate thereof is formed. The acyloxy, alkoxy and alkoxycarbonyloxy groups in R^{11} have preferably 1-3 carbon atoms.

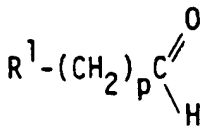
The reaction of a compound of the formula IV with a compound of the formula V is preferably effected by heating with a compound of the general formula V, wherein R^{11} represents a leaving group. For example the compound of the formula V may be an acid, an acid chloride, an acid anhydride, including a mixed anhydride of the acid $R^6(CR^4R^5)_nCOOH$ and a haloformate ester. The presence of an acid catalyst, e.g. HCl, may be necessary.

C. A compound of the general formula VII



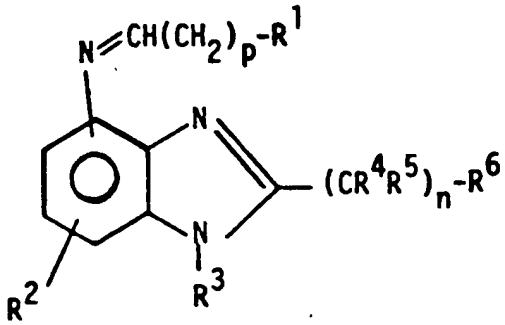
VII

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above is reacted with a compound of the general formula VIII



VIII

wherein R^1 is as defined above and p is an integer 0-5 to form a compound of the general formula IX



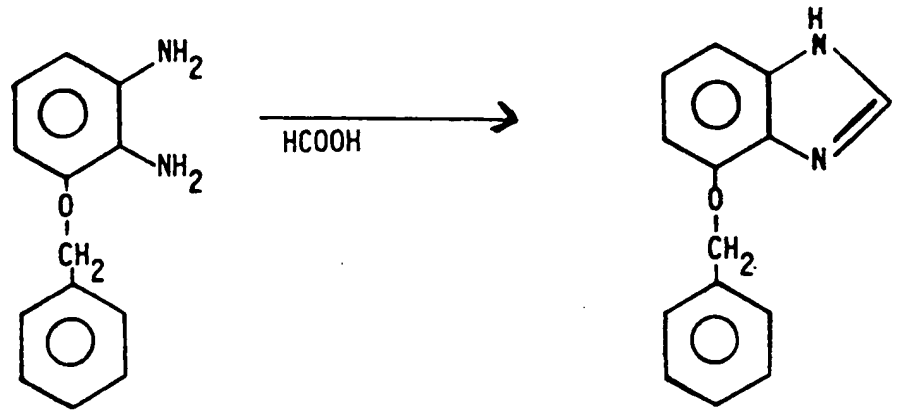
IX

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above and whereafter the compound of the formula IX is hydrogenated to a compound of the general formula I, wherein A is $-NR(CH_2)_m-$ and R^1, R^2, R^3, R^4, R^5 R^6, n and m are as defined above.

EXAMPLES

Example 1.

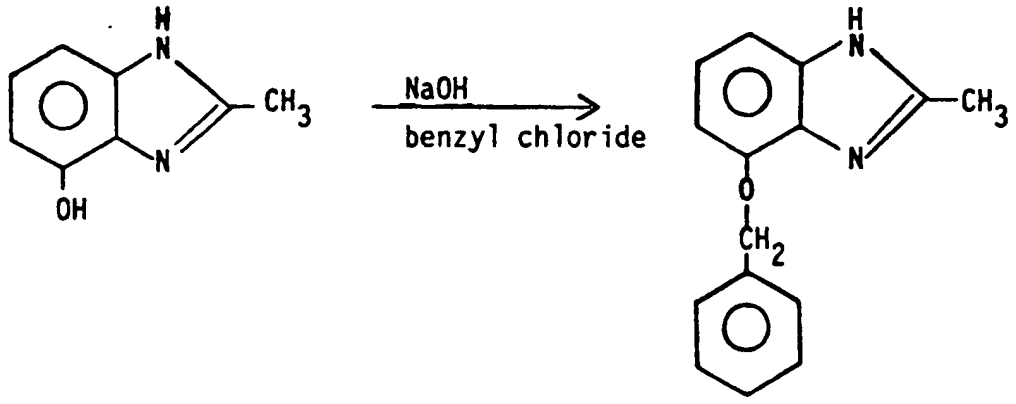
Preparation of 4-benzyloxybenzimidazole



A mixture of 3-benzyloxy-1,2-diaminobenzene 1.6 g (0.0073 mol) and formic acid (2.6 g, 0.057 mol) was heated to reflux for 1.5 h. The resulting mixture was then cooled, dissolved in methylene chloride, washed with 10% sodium carbonate solution, dried (Na_2SO_4) and evaporated to dryness in vacuo. The residue was recrystallized from acetonitrile to give the title compound in 0.75 g (46%) yield, m.p. 165-167 °C.

Example 2.

Preparation of 4-benzyloxy-2-methylbenzimidazole



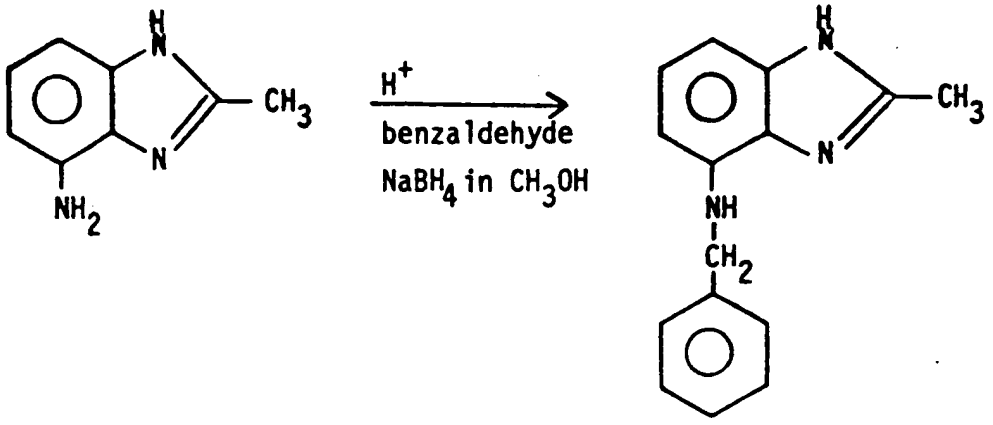
To a stirred solution of 7.3 g (0.049 mol) 4-hydroxy-2-methylbenzimidazole in 300 ml ethanol at ambient temperature 2.0 g (0.049 mol) NaOH in 4 ml water was added dropwise. The solution was stirred for 10 min and 6.3 g (0.049 mol) benzyl chloride was then added dropwise. The reaction mixture was heated under reflux for 20 h. Upon cooling to ambi ent temperature the volatiles were removed under reduced pressure. The residue obtained was dissolved in methylene chloride, washed with water and dried (Na_2SO_4). Following filtration, methylene chloride was removed under reduced pressure to give an oil. Chromatography on silica gel and elution with methylene chloride:methanol (10:1) gave 4.3 g (0.018 mol), yield: 37% of 4-benzyloxy-2-methylbenzimidazole m.p. 119-121 °C.

Examples 3-8.

In the same manner as described above the following compounds were obtained.
4-benzyloxy-2-ethylbenzimidazole
mp: 78-80 °C
yield: 33%
5-benzyloxy-2-methylbenzimidazole
mp: 165-165 °C
yield: 17%
4-(p-chlorobenzyloxy)-2-methylbenzimidazole
mp: 230-231 °C
yield: 7%
4-(p-fluorobenzyloxy)-2-methylbenzimidazole
mp: 203-205 °C
yield: 22%
4-benzyloxy-2-hydroxymethylbenzimidazole
mp: 146-147 °C
yield: 3%
2-methyl-4-phenylethoxybenzimidazole
mp: 176-178 °C
yield 15%

Example 9.

Preparation of 4-benzylamino-2-methylbenzimidazole

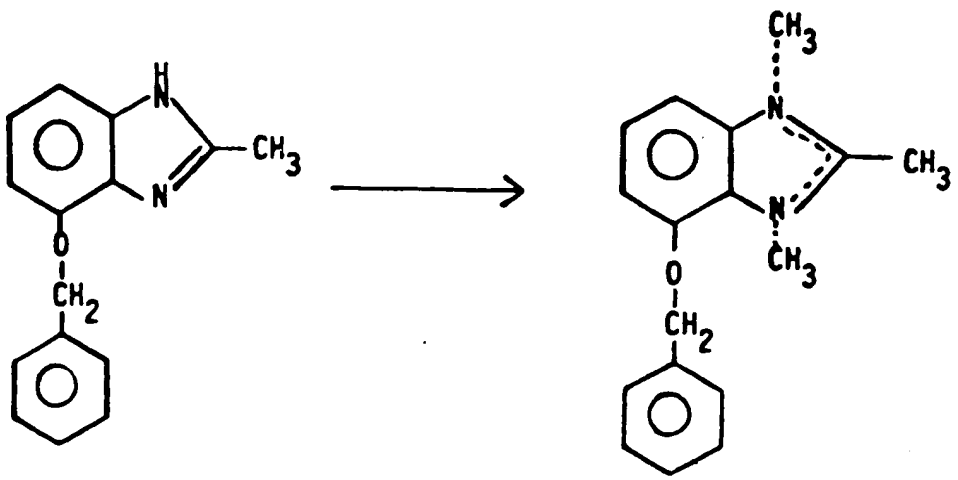


A mixture of 3.8 g (0.026 mol) 4-amino-2-methylbenzimidazole, 2.7 g (0.026 mol) benzaldehyde and 0.05 g paratoluene sulfonic acid in 250 ml toluene was refluxed and the water formed was separated during 20 h. Upon cooling the volatiles were removed under reduced pressure. The residue obtained was suspended in 150 ml methanol and 1.8 g (0.048 mol) $NaBH_4$ was added. The mixture was stirred at room temperature for 2h and methanol was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with water and dried (Na_2SO_4). After filtration, methylene chloride was removed under reduced pressure. Chromatography on silica gel and elution with methylene chloride:methanol (10:1) gave 0.1 g (0.00042 mol) of 4-benzylamino-2-methyl benzimidazole

NMR δ ($CDCl_3$) 2.45 (s,3H), 4.40 (s,2H), 6.30 (dd,1H), 6.70 (dd, 1H), 6.95 (dd,1H), 6.95 (dd,1H), 7.05-7.40 (m,5H).

Example 10.

Preparation of 4-benzyloxy-1,2-dimethylbenzimidazole and 7-benzyloxy-1,2-dimethylbenzimidazole



To a mixture of 0.5 g (0.021 mol) 4-benzyloxy-2-methylbenzimidazole 0.71 g (0.021 mol) tetrabutylammonium hydrogen sulfate and 0.48 g (0.0033 mol) methyl iodide in 30 ml methylene chloride and 0.17 g (0.0042 mol) NaOH in 30 ml H_2O was added dropwise with stirring. The mixture was heated to reflux for 2 h. Upon cooling the organic layer was separated and the volatiles were removed under reduced pressure to give an oil. The oil was suspended in ether, tetrabutylammonium iodide was filtered off and the volatiles were removed. Chromatography on silica gel and elution with methylene chloride methanol (10:1) gave 0.24 g (0.00095 mol) yield: 45% of the isomeric product 4-benzyloxy-1,2-dimethylbenzimidazole and 7-benzyloxy-1,2-dimethylbenzimidazole mp: 100-101 ° C.

The compounds 11-24 listed in the following Table 2 were prepared according to process A or B.

Table 2.

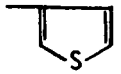
Summary of Examples 1-10

Process for prep.	Ex. No.	A	R^1	R^2	R^3	R^4	R^5	R^6	n	yield %	Identifying data
B	1	4-O-CH_2	phenyl	H	H	H	H	H	0	46	165-167°C
A	2	4-O-CH_2	phenyl	H	H	H	H	H	1	37	119-121°C
	3	4-O-CH_2	phenyl	H	H	H	H	H	2	33	78-80°C
	4	5-O-CH_2	phenyl	H	H	H	H	H	1	17	164-165°C
	5	4-O-CH_2	4'-Cl-phenyl	H	H	H	H	H	1	7	230-231°C
	6	4-O-CH_2	4'-F-phenyl	H	H	H	H	H	1	22	203-205°C
	7	4-O-CH_2	phenyl	H	H	H	H	OH	1	3	146-147°C
	8	4-O-CH_2CH_2	phenyl	H	H	H	H	H	1	15	176-178°C
C	9	4-NH-CH_2	phenyl	H	H	H	H	H	1	2	NMR
	10	4-O-CH_2	phenyl	H	CH_3	H	H	H	1?	45	100-101
		7-OCH_2	phenyl	H	CH_3	H	H	H	1)		(isomeric mixture)

cont.

cont.

Table 2.

Process for prep.	Ex. No.	A	R^1	R^2	R^3	R^4	R^5	R^6	n	yield %	Identifying data
B	11	4-OCH_2	phenyl	H	H	H	H	phenyl	1	2	NMR
B	12	4-OCH_2	2,'4'-di-Cl-phenyl	H	H	H	H	H	1	33	205-207°C
B	13	4-OCH_2	2,'4'-di-F-phenyl	H	H	H	H	H	1	27	190-192°C
B	14	5-OCH_2	4'-F-phenyl	H	H	H	H	H	1	9	79-80°C
A	15	4-OCH_2		H	H	H	H	H	1	2	155-156°C
A	16	4-OCH_2	3'-F-phenyl	H	H	H	H	H	1	18	140°C (HCl salt)
B	17	4-OCH_2	2'-F-phenyl	H	H	H	H	H	1	23	148°C
A	18	4-OCH_2	phenyl	-	H	-	-	NH_2	0	13	NMR
A	19	4-OCH_2	cyklohexyl	H	H	H	H	H	1	23	128-130°C
A	20	4-$NHCH_2$	cyklohexyl	H	H	H	H	H	1	2	90°C
A	21	4-$N(CH_2$-$C_6H_5)CH_2$	phenyl	H	H	H	H	H	1	11	NMR
A	22	4-OCH_2	phenyl	H	CH_2CH_2-C_6H_5	H	H	H	1	6	(isomeric mixture) NMR
		7-OCH_2	phenyl	H	CH_2CH_2-C_6H_5	H	H	H	1		

cont.

cont.

Table 2.

Process for prep.	Ex. No.	A	R^1	R^2	R^3	R^4	R^5	R^6	n	yield %	Identifying data
A	23	4-OCH_2	phenyl	H	H	H	H	$N(CH_3)_2$	0	20	208°C
B	24	5-OCH_2CH_2	phenyl	H	H	H	H	H	1	25	139°C

^{1}H NMR-data for compounds 11, 18, 21, and 22 are given in the following Table 3.

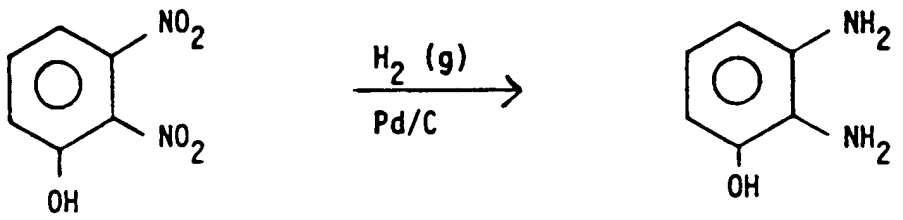
Table 3 ^{1}H NMR

Compound No.	Solvent	NMR δ
11	$CDCl_3$	4.0 (s, 2H), 5.15 (s, 2H), 6.75 (d, 1H), 7.0-7.4 (m, 7H)
18	CD_3OD	5.25 (s, 2H), 6.8 (d, 1H), 7.05 (t, 1H), 7.35-7.45 (m, 3H), 7.6 (d, 2H)
21	DMSO	2.45 (s, 3H), 4.9 (s, 4H), 6.25 (d, 1H), J=8Hz, 6.8 (m, 2H), 7.2 (m, 2H), 7.25 (s(broad), 8H)
22	$CDCl_3$	2.15 (s, 3H), 2.25 (s, 3H), 3.0 (t, 2H), 3.1 (t, 2H), 4.3 (t, 2H), 4.45 (t, 2H), 5.25 (s, 2H), 5.35 (s, 2H), 6.7 (d, 1H), 6.75 (dd, 2H), 6.85 (d, 1H), 6.9 (d, 1H), 7.0 (dd, 2H) 7.1-7.2 (m, 5H), 7.25-7.4 (m, 10H), 7.5-7.6 (m, 4H)

The following examples illustrate intermediates useful in the preparation of the compounds examplified in Examples 1-10 and Table 1.

Example I

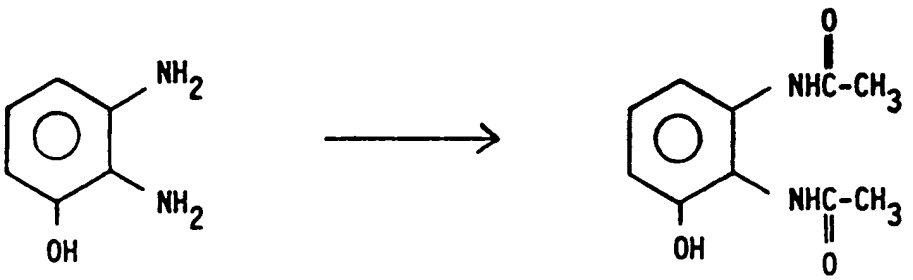
Preparation of 2,3-diaminophenol



2,3-dinitrophenol (80%) 25 g (0.11 mol) was dissolved in 700 ml ethanol and 0.5 g Pd/C was added. The mixture was hydrogenated at room temperature until the uptake of hydrogen ceased (4h). The solution was filtered (celite) in N_2-atmosphere and evaporated to dryness in vacuo to give the title compound as an unstable oil (18 g), which was used immediately for the next step.

Example II

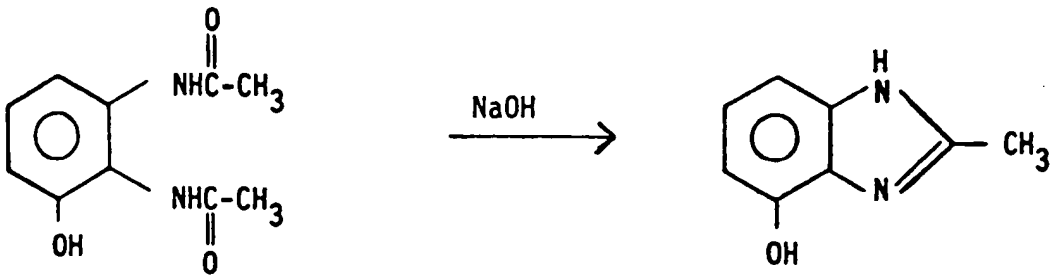
Preparation of 2,3-diacetamidophenol



To 18 g (0.11 mol) 2,3-diaminophenol obtained according to Example I 38 ml (0.40 mol) of acetic anhydride was added. The mixture was stirred for 45 min and 50 ml ice and water were added. After stirring for 30 min the product was filtered off and dried to give (15.8 g) of the title compound.

Example III

Preparation of 4-hydroxy-2-methylbenzimidazole

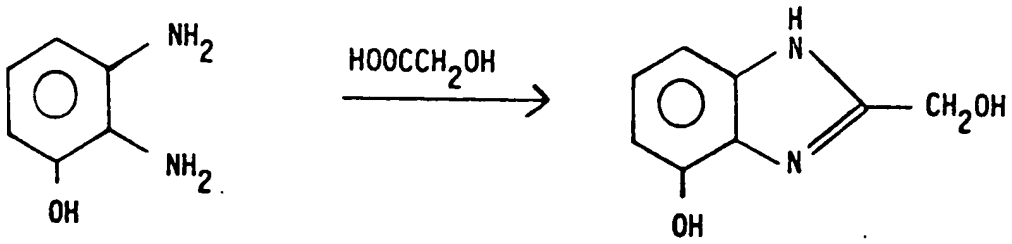


To a solution of 6.8 M NaOH 15.8 g (0.076 mol) of 2,3-diacetamidophenol was added and the mixture was heated under reflux for 2h. Upon cooling the pH of the solution was adjusted to 8.5 with 2 M HCl. The

solid was filtered off, washed with water and dried to give 7.6 g of the title compound.

Example IV

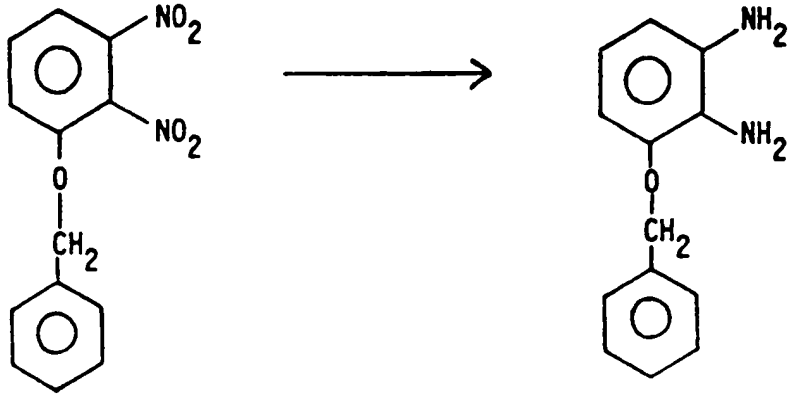
Preparation of 4-hydroxy-2-hydroxymethylbenzimidazole



To a solution of 40 ml 4 M HCl 1.1 g (0.0087 mol) of 2,3-diaminophenol and 2 g (0.026 mol) of glycolic acid were added and the solution was heated under reflux for 20 h. Upon cooling the reaction mixture was alkalized with 10 M NaOH to pH 8.5. The volatiles were removed under reduced pressure and the residual oil was suspended in methanol. The suspension was filtered and evaporated to dryness in vacuo. Chromatography on silica gel and elution with methylene chloride:methanol (10:2) gave 0.78 g of the title compound.

Example V

Preparation of 3-benzyloxy-1,2-diaminobenzene



To a solution of 3-benzyloxy-1,2-dinitrobenzene (2 g 0.0073 mol) in 300 ml ethanol Raney-nickel (1 g) was added and the mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased (30 min). The colourless solution was filtered (celite) and evaporated to dryness in vacuo to give the title compound as an unstable oil (1.6 g) which was used immediately for the next step.

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelating,

or another suitable carrier, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. An enteric coating which protects the active compound from acid degradation as long as the dosage form remains in the stomach may be wanted. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may als o contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine. The hard gelating capsules may be enteric coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solution or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugaralcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to by reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

Pharmaceutical preparations containing a compound of the invention as active ingredient are illustrated in the following examples.

Example 11. Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

4-Benzyloxy-2-methylbenzimidazole	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the acid addition salt was dissolved in the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 12. Enteric-coated tablets

An enteric-coated tablet containing 20 mg of active compound was prepared from the following ingredients:

I	4-(p-Fluorobenzyloxy)-2-methyl-benzimidazole	200 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I 4-(p-Fluorobenzyloxy)-2-methyl-benzimidazole,powder, was mixed with lactose and cross-linked polyvinylpyrrolidone and granu lated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 20 mg of active substance, in a tabletting machine using 6 mm diameter punches.
II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota®, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Example 13. Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

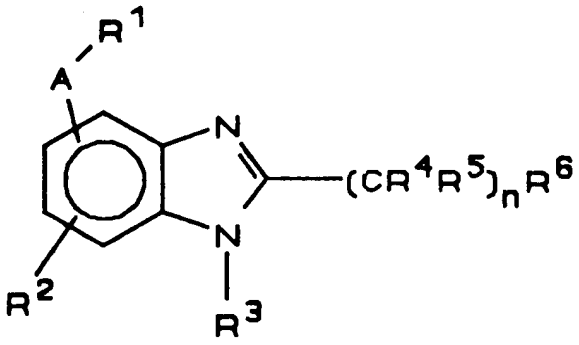
4-(p-Chlorobenzyloxy)-2-methylbenzimidazole	4 g
Polyethylene glycol 400 for injection	400 g
Disodium hydrogen phosphate	q.s.
Sterile water to a final volume of	1000 ml

4-(p-Chlorobenzyloxy)-2-methylbenzimidazole was dissolved in polyethylene glycol 400 and 550 ml of water was added. pH of the solution was brought to pH 7.4 by adding a water solution of disodium hydrogen phosphate and water was added to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Claims

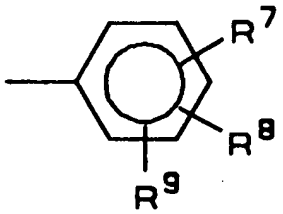
Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of the general formula I



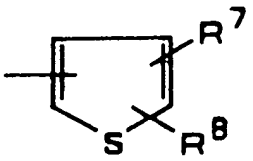
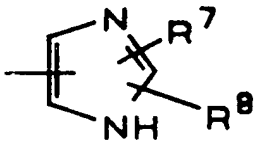
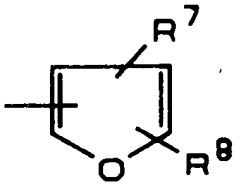
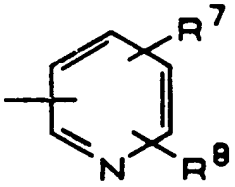
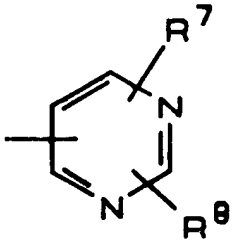
I

or a pharmaceutically acceptable salt or solvate thereof, in which
R^1 represents a substituted or unsubstituted aryl group of the formula II'



II'

in which each of R^7, R^8, R^9 independently represents hydrogen, an alkyl having up to 6 carbon atoms, an alkoxy having up to 6 carbon atoms, halogen, preferably chloro or fluoro, or a heterocyclic aryl group of one of the following formulas

in which R^7 and R^8 have the meanings given above;
or a cycloalkyl group with 3-8 carbon atoms in the unsubstituted cyclic group; or an adamantyl group;
R^2 represents hydrogen, an alkyl containing up to 6 carbon atoms, an alkoxy containing up to 6 carbon atoms, or halogen;
R^3 represents hydrogen, an alkyl containing up to 6 carbon atoms, a phenylalkyl with 1-4 carbon atoms in the alkyl group or a cycloalkyl-alkyl group with 3-8 carbon atoms in the cyclic group and 1-4 carbon atoms in the alkyl group;
n is an integer 0-6;
R^4 represents hydrogen or an alkyl containing up to 6 carbon atoms;
R^5 represents hydrogen or an alkyl containing up to 6 carbon atoms;
R^6 represents hydrogen, an alkyl containing up to 6 carbon atoms, a substituted or unsubstituted aryl group as defined above for R^1 or when n is 1-6 a hydroxyl group or when n is 0 an amino, an alkylamino or a dialkylamino group with 1-4 carbon atoms in the alkyl groups;
A represents an alkylene up to 6 carbon atoms, optionally connected to, or interrupted by an optionally substituted hetero atom selected from O, S, and NR, wherein R is hydrogen, an alkyl containing up to 6 carbon atoms, a phenylalkyl with 1-4 carbon atoms in the alkyl group or a cycloalkyl-alkyl group with 3-8 carbon atoms in the cyclic group and 1-4 carbon atoms in the alkyl group; or an alkenylene with up to 6 carbon atoms
with the provisos that when
a) n is 0 and R^2, R^3 and R^6 are all hydrogen, then the group A-R^1 is not 7-benzylamino or 7-(4'-methoxy)-benzylamino; and when
b) n is 1 and R^3, R^4 and R^5 are all hydrogen, R^2 is 4-methyl, R^6 is ethyl, phenyl, benzyl, or (4'-methoxy)-phenyl then the group A-R^1 is not 7-benzyloxy; and when
c) n is 0, R^2 is 4-methyl, R^3 is hydrogen and R^6 is phenyl, than the group A-R^1 is not 7-benzyloxy.

2. A compound of the general formula I according to claim 1 wherein
R^1 is as defined above
R^2 represents hydrogen, an alkyl with 1-6 carbon atoms, an alkoxy with 1-6 carbon atoms, chloro, bromo or fluoro;
R^3, R^4 and R^5 are the same or different and represent hydrogen or an alkyl with 1-6 carbon atoms;
R^6 represents hydrogen, a alkyl with 1-6 carbon atoms, a hydroxyl group or a substituted or

unsubstituted aryl group as defined above for R^1, whereby R^1 and R^6 are the same or different;
n is an integer 0-6;
A represents an alkylene with up to 6 carbon atoms, optionally connected to or interrupted by an eventually substituted hetero atom selected from O, S and NR, wherein R is hydrogen or a alkyl with 1-6 carbon atoms; or an alkenylene with up to 6 carbon atoms.

3. A compound according to claim 1 wherein A is $-O-CH_2-$, R^1 is phenyl, R^2, R^3, R^4, R^5 and R^6 are all hydrogen and n is 1.

4. A compound according to claim 1 wherein A is $-O-CH_2-$, R^1 is phenyl, R^3 is methyl, R^2, R^4, R^5 and R^6 are all hydrogen and n is 1.

5. A pharmaceutical composition containing as active ingredient a compound according to any of claims 1-4.

6. A compound as defined in any of claims 1-4, or a therapeutically acceptable salt thereof, for use in inhibiting gastric acid secretion in mammals and man.

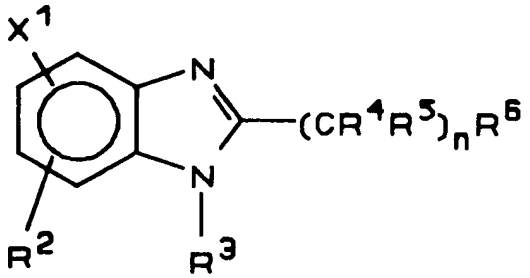
7. A compound as defined in any of claims 1-4, or a therapeutically acceptale salt thereof, for use as gastrointestinal cytoprotecting agent in mammals and man.

8. A compound as defined in any of claims 1-4, or a therapeutically acceptable salt thereof, for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

9. Use of a compound of the general formula I according to claim 1 without the provisos a) - c) in the preparation of a pharmaceutical composition with inhibiting effect of gastric acid secretion.

10. Use of a compound as defined in claim 9 in the preparation of a pharmaceutical composition with antiinflammatory effect on gastrointestinal inflammatory diseases.

11. A process for the preparation of a compound of the formula I according to claim 1 by
A. Reacting a compound of the general formula II



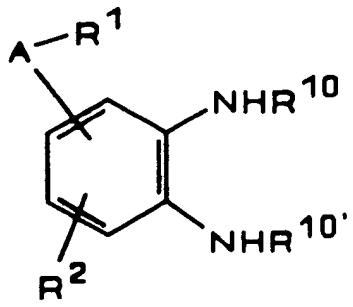
II

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above with a compound of the formula III

$R^1(CH_2)_mX^2$ III

wherein R^1 is as defined above, X^1 is -OH, -SH, or -NHR and X^2 is a leaving group, whereby a compound of the general formula I, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above and m is an integer 1-6 and A is $-O(CH_2)_m$, $-S(CH_2)_m$, or $-NR(CH_2)_m$, is obtained;

B. Reacting a compound of the general formula IV

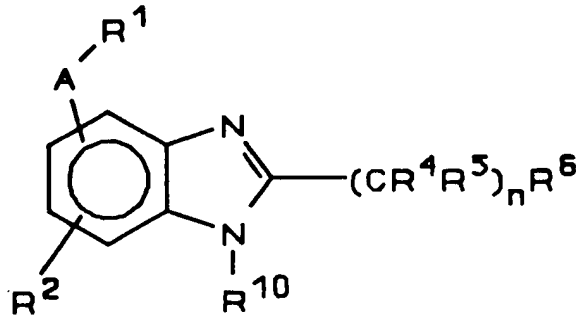


IV

wherein R^1 and R^2 are as defined above, R^{10} and $R^{10'}$ are the same or different and each is hydrogen, a lower alkyl group having up to 6 carbon atoms or a group or atom convertible to a lower alkyl group with the proviso that when one of R^{10} and $R^{10'}$ is a lower alkyl group or a group or atom convertible to a lower alkyl group the other of R^{10} and $R^{10'}$ is hydrogen with a compound of the general formula V

$R^6(CR^4R^5)_nCOR^{11}$ V

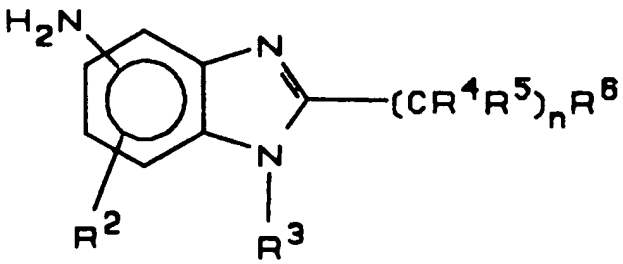
wherein R^4, R^5, R^6 and n are as defined above and R^{11} is a leaving group or hydrogen, whereby a compound of the general formula VI



VI

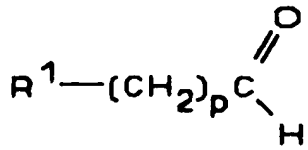
is formed and, if required, a nitrogen atom of the benzimidazole nucleus is alkylated and, if required, protecting groups are removed, to form a compound of the general formula I, and if required a salt or solvate thereof is formed; or

C. Reacting a compound of the general formula VII



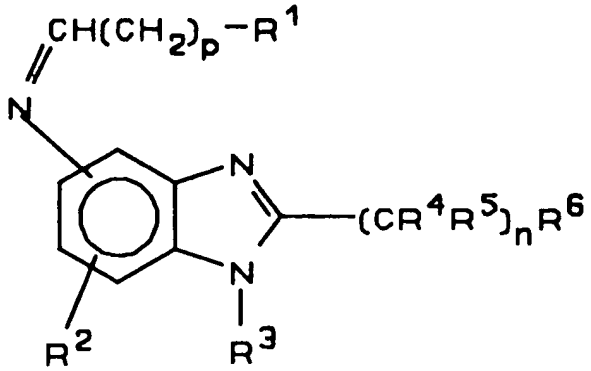
VII

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above with a compound of the general formula VIII



VIII

wherein R^1 is as defined above and p is an integer 0-5 to form a compound of the general formula IX

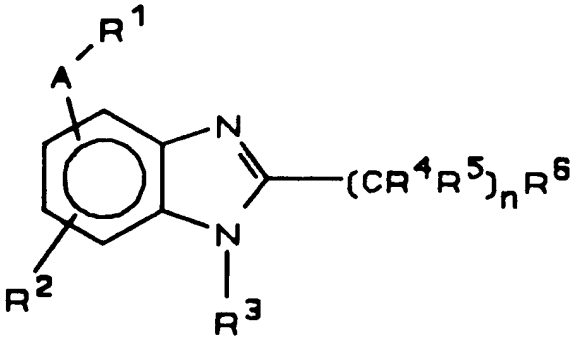


IX

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above, and whereafter the compound of the formula IX is hydrogenated to a compound of the general formula I, wherein A is $-NR(CH_2)_m-$ and R^1, R^2, R^3, R^4, R^5 and R^6, n and m are as defined above.

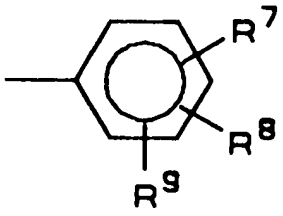
Claims for the following Contracting State : ES

1. A process for the preparation of a compound of the general formula I



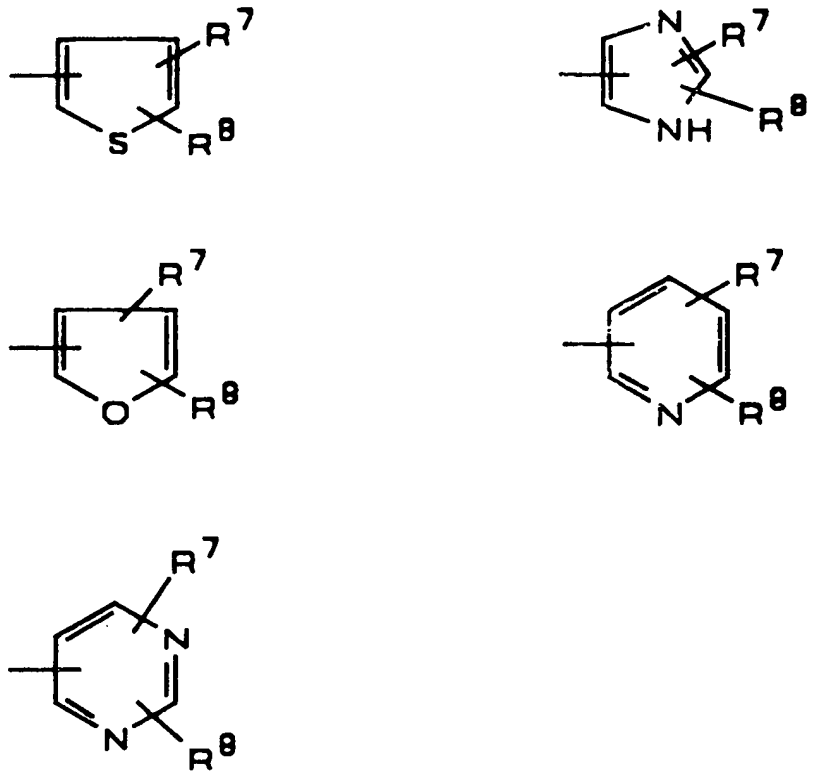
I

or a pharmaceutically acceptable salt or solvate thereof, in which
R^1 represents a substituted or unsubstituted aryl group of the formula II'



II'

in which each of R^7, R^8, R^9 independently represents hydrogen, a lower alkyl having up to 6 carbon atoms, a lower alkoxy having up to 6 carbon atoms, halogen, preferably chloro or fluoro, or a heterocyclic aryl group of one of the following formulas



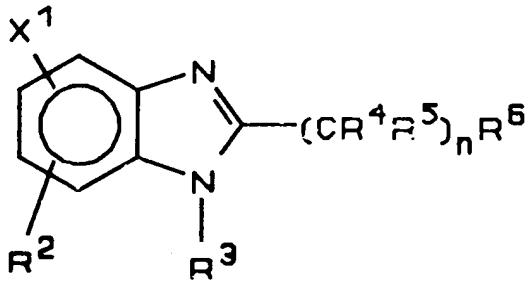
in which R^7 and R^8 have the meanings given above;
or a cycloalkyl group with 3-8 carbon atoms in the unsubstituted cyclic group; or an adamantyl group;
R^2 represents hydrogen, a lower alkyl containing up to 6 carbon atoms, a lower alkoxy containing up to 6 carbon atoms, or halogen;
R^3 represents hydrogen, a lower alkyl containing up to 6 carbon atoms, a phenylalkyl with 1-4 carbon atoms in the alkyl group or a cycloalkyl-alkyl group with 3-8 carbon atoms in the cyclic group and 1-4 carbon atoms in the alkyl group;
n is an integer 0-6;
R^4 represents hydrogen or a lower alkyl containing up to 6 carbon atoms;
R^5 represents hydrogen or a lower alkyl containing up to 6 carbon atoms;
R^6 represents hydrogen, a lower alkyl containing up to 6 carbon atoms, a substituted or unsubstituted aryl group as defined above for R^1 or when n is 1-6 a hydroxyl group or when n is 0 an amino, an alkylamino or a dialkylamino group with 1-4 carbon atoms in the alkyl groups;
A represents an alkylene, optionally connected to, or interrupted by an optionally substituted hetero atom selected from O, S, and NR, wherein R is hydrogen, a lower alkyl containing up to 6 carbon atoms, a phenylalkyl with 1-4 carbon atoms in the alkyl group or a cycloalkyl-alkyl group with 3-8 carbon atoms in the cyclic group and 1-4 carbon atoms in the alkyl group; or an alkenylene
with the provisos that when

a) n is 0 and R^2, R^3 and R^5 are all hydrogen, then the group A-R^1 is not 7-benzylamino or 7-(4'-methoxy)-benzylamino; and when

b) n is 1 and R^3, R^4 and R^5 are all hydrogen, R^2 is 4-methyl, R^6 is ethyl, phenyl, benzyl, or (4'-methoxy)-phenyl then the group A-R^1 is not 7-benzyloxy; and when

c) n is 0, R^2 is 4-methyl, R^3 is hydrogen and R^6 is phenyl, then the group A-R^1 is not 7-benzyloxy.

A. Reacting a compound of the general formula II

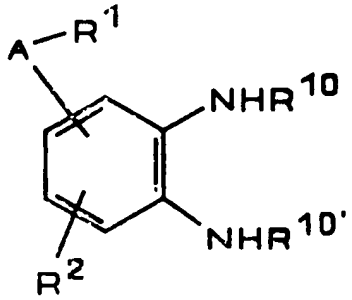


II

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above with a compound of the formula III

$R^1(CH_2)_mX^2$ III

wherein R^1 is as defined above, X^1 is -OH, -SH, or -NHR and X^2 is a leaving group, whereby a compound of the general formula I, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above and m is an integer 1-6 and A is $-O(CH_2)_m$, $-S(CH_2)_m$, or $-NR(CH_2)_m$, is obtained;
B. Reacting a compound of the general formula IV

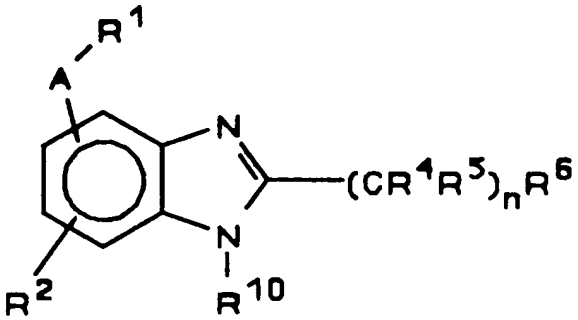


IV

wherein R^1 and R^2 are as defined above, R^{10} and $R^{10'}$ are the same or different and each is hydrogen, a lower alkyl group having up to 6 carbon atoms or a group or atom convertible to a lower alkyl group with the proviso that when one of R^{10} and $R^{10'}$ is a lower alkyl group or a group or atom convertible to a lower alkyl group the other of R^{10} and $R^{10'}$ is hydrogen with a compound of the general formula V

$R^6(CR^4R^5)_nCOR^{11}$ V

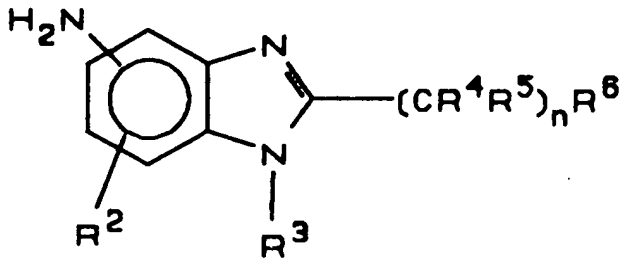
wherein R^4, R^5, R^6 and n are as defined above and R^{11} is a leaving group or hydrogen, whereby a compound of the general formula VI



VI

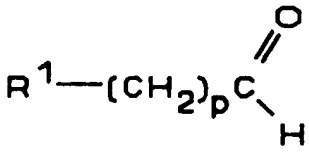
is formed and, if required, a nitrogen atom of the benzimidazole nucleus is alkylated and, if required, protecting groups are removed, to form a compound of the general formula I, and if required a salt or solvate thereof is formed; or

C. Reacting a compound of the general formula VII



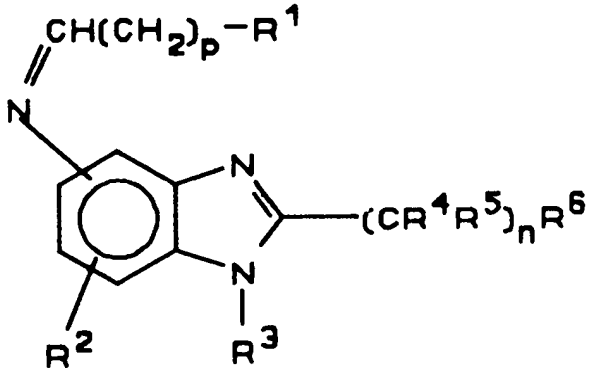
VII

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above with a compound of the general formula VIII



VIII

wherein R^1 is as defined above and p is an integer 0-5 to form a compound of the general formula IX



IX

wherein R^2, R^3, R^4, R^5 and R^6 are as defined above, and whereafter the compound of the formula IX is hydrogenated to a compound of the general formula I, wherein A is $-NR(CH_2)_m-$ and R^1, R^2, R^3, R^4, R^5 and R^6, n and m are as defined above.

2. A process according to claim 1 wherein in the compound of the general formula I

R^1 is as defined above;

R^2 represents hydrogen, a lower alkyl with 1-6 carbon atoms, a lower alkoxy with 1-6 carbon atoms, chloro, bromo or fluoro;

R^3, R^4 and R^5 are the same or different and represent hydrogen or a lower alkyl with 1-6 carbon atoms;

R^6 represents hydrogen, a lower alkyl with 1-6 carbon atoms, a hydroxyl group or a substituted or unsubstituted aryl group as defined above for R^1, whereby R^1 and R^6 are the same or different;

n is an integer 0-6;

A represents an alkylene with up to 6 carbon atoms, optionally connected to or interrupted by an eventually substituted hetero atom selected from O, S and NR, wherein R is hydrogen or a lower alkyl with 1-6 carbon atoms; or an alkenylene with up to 6 carbon atoms.

3. A process according to claim 1 wherein A is $-O-CH_2-$, R^1 is phenyl, R^2, R^3, R^4, R^5 and R^6 are all hydrogen and n is 1.

4. A process according to claim 1 wherein A is $-O-CH_2-$, R^1 is phenyl. R^3 is methyl, R^2, R^3, R^4, R^5 and R^6 are all hydrogen and n is 1.

5. A process for the preparation of a pharmaceutical composition characterized in that it contains a compound produced according to any of claims 1-4 as the active ingredient.

6. A process according to claim 1, characterized in that the compound of the formula I, or a therapeutically acceptable salt thereof, is used in inhibiting gastric acid secretion in mammals and man.

7. A process according to claim 1, characterized in that the compound of the formula I, or a therapeutically acceptable salt thereof, is used as gastrointestinal cytoprotecting agent in mammals and man.

8. A process according to claim 1, characterized in that the compound of the general formula I, or a therapeutically acceptable salt thereof, is used in the treatment of gastrointestinal inflammatory diseases in mammals and man.

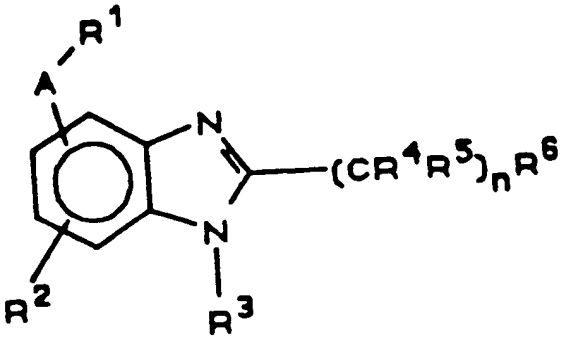
9. Use of a compound of the general formula I according to claim 1 without the provisos a) - c) in the preparation of a pharmaceutical composition with inhibiting effect of gastric acid secretion.

10. Use of a compound as defined in claim 9 in the preparation of a pharmaceutical composition with antiinflammatory effect on gastrointestinal inflammatory diseases.

Patentansprüche

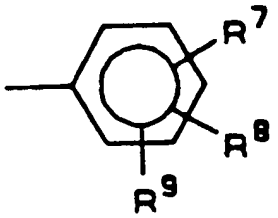
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Verbindung der allgemeinen Formel I



I

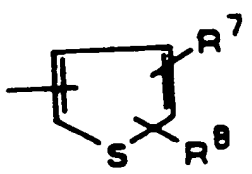
oder ein pharmazeutisch akzeptables Salz oder Solvat hievon, worin
R^1 eine substituierte oder unsubstituierte Arylgruppe der Formel II'

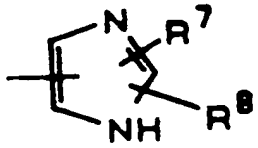


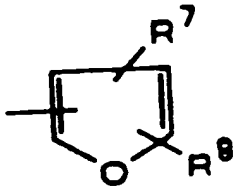
II'

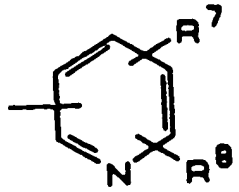
worin R^7, R^8, R^9 jeweils unabhängig voneinander Wasserstoff, ein Alkyl mit bis zu 6 Kohlenstoffatomen, ein Alkoxy mit bis zu 6 Kohlenstoffatomen, Halogen, vorzugsweise Chlor oder Fluor, bedeutet, oder

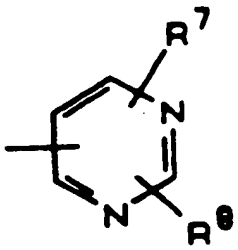
eine heterocyclische Arylgruppe einer der folgenden Formeln











,

worin R^7 und R^8 die oben angegebene Bedeutung haben; oder eine Cycloalkylgruppe mit 3-8 Kohlenstoffatomen in der unsubstituierten cyclischen Gruppe; oder eine Adamantylgruppe darstellt;
R^2 Wasserstoff, ein Alkyl mit bis zu 6 Kohlenstoffatomen, ein Alkoxy mit bis zu 6 Kohlenstoffatomen, oder Halogen darstellt;
R^3 Wasserstoff, ein Alkyl mit bis zu 6 Kohlenstoffatomen, ein Phenylalkyl mit 1-4 Kohlenstoffatomen in der Alkylgruppe oder eine Cycloalkyl-Alkylgruppe mit 3-8 Kohlenstoffatomen in der cyclischen Gruppe und 1-4 Kohlenstoffatomen in der Alkylgruppe darstellt;
n eine ganze Zahl 0-6 bedeutet;
R^4 Wasserstoff oder ein Alkyl mit bis zu 6 Kohlenstoffatomen darstellt;
R^5 Wasserstoff oder ein Alkyl mit bis zu 6 Kohlenstoffatomen darstellt;
R^6 Wasserstoff, ein Alkyl mit bis zu 6 Kohlenstoffatomen, eine substituierte oder unsubstituierte Arylgruppe, wie für R^1 definiert, darstellt, oder, weg n 1-6 bedeutet, eine Hydroxylgruppe, oder, wenn n 0 bedeutet, eine Amino-, eine Alkylamino- oder eine Dialkylaminogruppe mit 1-4 Kohlenstoffatomen in den Alkylgruppen darstellt;
A ein Alkylen mit bis zu 6 Kohlenstoffatomen, gegebenenfalls verbunden mit oder unterbrochen durch ein gegebenenfalls substituiertes Heteroatom ausgewählt aus O, S und NR, worin R Wasserstoff, ein Alkyl mit bis zu 6 Kohlenstoffatomen, ein Phenylalkyl mit 1-4 Kohlenstoffatomen in der Alkylgruppe oder eine Cycloalkyl-alkyl-gruppe mit 3-8 Kohlenstoffatomen in der cyclischen Gruppe und 1-4 Kohlenstoffatomen in der Alkylgruppe; oder ein Alkylen mit bis zu 6 Kohlenstoffatomen darstellt;
mit der Maßgabe, daß wenn

a) n 0 ist und R^2, R^3 und R^6 alle Wasserstoff bedeuten, die Gruppe A-R^1 nicht 7-Benzylamino oder 7-(4'-Methoxy)-benzylamino ist; und wenn

b) n 1 ist, R^3, R^4 und R^5 alle Wasserstoff bedeuten, R^2 4-Methyl ist und R^6 Ethyl, Phenyl, Benzyl oder (4'-Methoxy)-phenyl bedeutet, die Gruppe A-R^1 nicht 7-Benzyloxy ist; und wenn

c) n 0 ist, R^2 4-Methyl bedeutet, R^3 Wasserstoff bedeutet und R^6 Phenyl darstellt, die Gruppe A-R^1 nicht 7-Benzyloxy ist.

2. Verbindung der allgemeinen Formel I nach Anspruch 1, worin R^1 die obige Bedeutung hat,
R^2 Wasserstoff, ein Alkyl mit 1-6 Kohlenstoffatomen, ein Alkoxy mit 1-6 Kohlenstoffatomen, Chlor, Brom

oder Fluor darstellt;
R^3, R^4 und R^5 gleich oder verschieden sind und Wasserstoff oder an Alkyl mit 1-6 Kohlenstoffatomen darstellen;
R^6 Wasserstoff, ein Alkyl mit 1-6 Kohlenstoffatomen, eine Hydroxylgruppe oder eine substituierte oder unsubstituierte Arylgruppe, wie oben für R^1 definiert, darstellt, wobei R^1 und R^6 gleich oder verschieden sind;
n eine ganze Zahl 0-6 ist;
A ein Alkylen mit bis zu 6 Kohlenstoffatomen, gegebenenfalls verbunden mit oder unterbrochen durch ein eventuell substituiertes Heteroatom ausgewählt aus O, S und NR, worin R Wasserstoff oder ein Alkyl mit 1-6 Kohlenstoffatomen ist; oder ein Alkenylen mit bis zu 6 Kohlenstoffatomen darstellt.

3. Verbindung nach Anspruch 1, worin A für $-O-CH_2-$ steht; R^1 Phenyl bedeutet, R^2, R^3, R^4, R^5 und R^6 alle Wasserstoff sind und n 1 ist.

4. Verbindung nach Anspruch 1, worin A für $-O-CH_2-$ steht, R^1 Phenyl bedeutet, R^3 Methyl ist, R^2, R^4, R^5 und R^6 alle Wasserstoff sind und n 1 ist.

5. Pharmazeutische Zusammensetzung, die als aktives Ingrediens eine Verbindung nach einem der Ansprüche 1-4 enthält.

6. Verbindung nach einem der Ansprüche 1-4 oder ein therapeutisch akzeptables Salz hievon zur Verwendung zur Hemmung der Magensäuresekretion bei Säugern und dem Menschen.

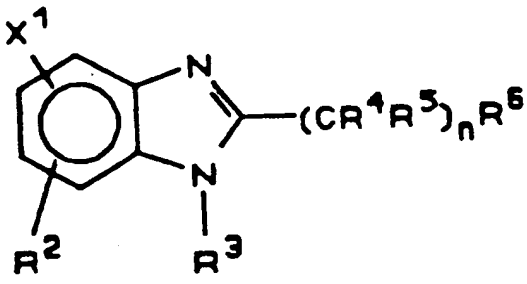
7. Verbindung nach einem der Ansprüche 1-4 oder ein therapeutisch akzeptables Salz hievon zur Verwendung als gastrointestinales Zellschutzmittel bei Säugern und dem Menschen.

8. Verbindung nach einem der Ansprüche 1-4 oder ein therapeutisch akzeptables Salz hievon zur Verwendung bei der Behandlung entzündlicher Erkrankungen des Magendarmtraktes bei Säugern und dem Menschen.

9. Verwendung einer Verbindung der allgemeinen Formel I nach Anspruch 1 ohne die Maßgaben a) - c) bei der Herstellung einer pharmazeutischen Zusammensetzung mit Hemmwirkung auf die Magensäuresekretion.

10. Verwendung einer Verbindung nach Anspruch 9 bei der Herstellung einer pharmazeutischen Zusammensetzung mit entzündungshemmender Wirkung auf entzündliche Erkrankungen des Magendarmtraktes.

11. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1 durch
A. Umsetzung einer Verbindung der allgemeinen Formel II



II ,

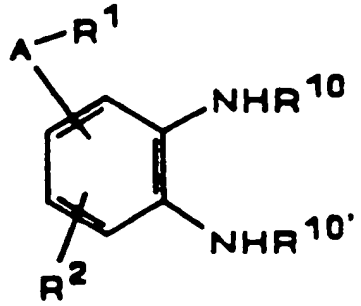
worin R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben, mit einer Verbindung der Formel III

$R^1(CH_2)_mX^2$ III,

worin R^1 die obige Bedeutung hat, X^1 für -OH, -SH oder -NHR steht und X^2 eine austretende Gruppe

ist, wodurch eine Verbindung der allgemeinen Formel I, worin R^1, R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben und m eine ganze Zahl 1-6 ist und A für $-O(CH_2)_m$, $-S(CH_2)_m$ oder $-NR(CH_2)_m$ steht,
erhalten wird;

B. Umsetzung einer Verbindung der allgemeinen Formel IV

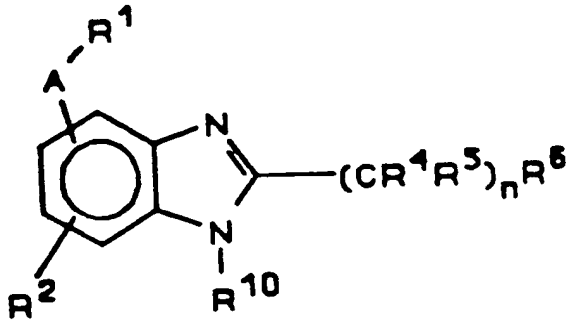


IV

worin R^1 und R^2 die obige Bedeutung haben, R^{10} und $R^{10'}$ gleich oder verschieden sind und jeweils Wasserstoff, eine Niedrigalkylgruppe mit bis zu 6 Kohlenstoffatomen oder eine Gruppe oder ein Atom bedeuten, die (das) in eine Niedrigalkylgruppe überführbar ist, mit der Maßgabe, daß wenn eines von R^{10} und $R^{10'}$ eine Niedrigalkylgruppe oder eine Gruppe oder ein Atom, die (das) in eine Niedrigalkylgruppe überführbar ist, bedeutet, das andere von R^{10} und $R^{10'}$ Wasserstoff ist, mit einer Verbindung der allgemeinen Formel V

$$R^5(CR^4R^5)_nCOR^{11} \qquad V,$$

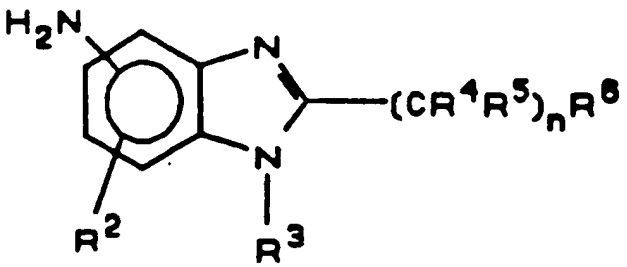
worin R^4, R^5, R^6 und n die obige Bedeutung haben und R^{11} eine austretende Gruppe oder Wasserstoff bedeutet, wodurch eine Verbindung der allgemeinen Formel VI



VI

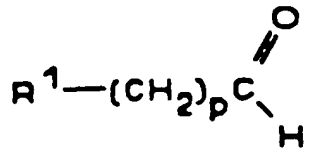
gebildet wird, und nötigenfalls ein Stickstoffatom des Benzimidazolkerns alkyliert und nötigenfalls Schutzgruppen entfernt werden, um eine Verbindung der allgemeinen Formel I zu erhalten, und nötigenfalls ein Salz oder Solvat hievon gebildet wird; oder

C. Umsetzung einer Verbindung der allgemeinen Formel VII



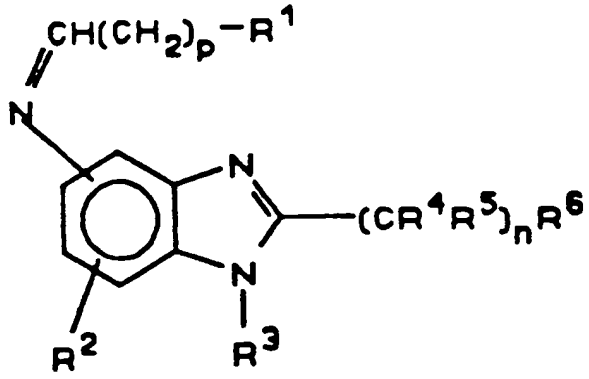
VII

worin R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben, mit einer Verbindung der allgemeinen Formel VIII



VIII

worin R^1 die obige Bedeutung hat und p eine ganze Zahl 0-5 ist, zur Bildung einer Verbindung der allgemeinen Formel IX

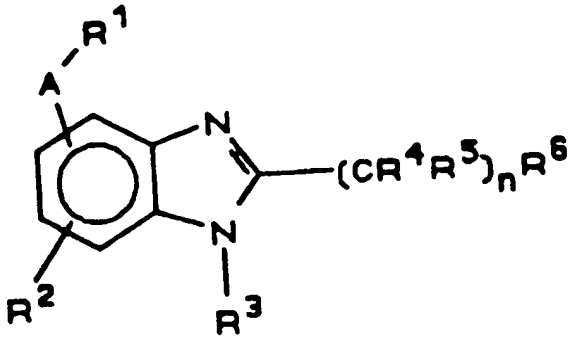


IX

worin R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben, und nachfolgende Hydrierung der Verbindung der Formel IX zu einer Verbindung der allgemeinen Formel I, worin A für $-NR(CH_2)_m-$ bedeutet und R^1, R^2, R^3, R^4, R^5 und R^6, n und m die obige Bedeutung haben.

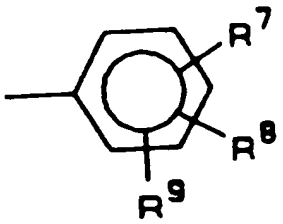
Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel I



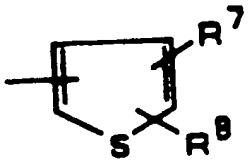
I

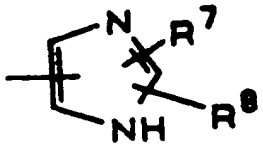
oder eines pharmazeutisch akzeptablen Salzes oder Solvats hievon, worin
R^1 eine substituierte oder unsubstituierte Arylgruppe der Formel II'

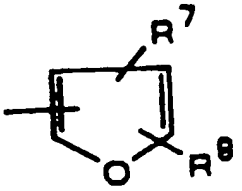


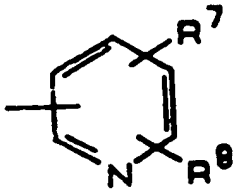
II'

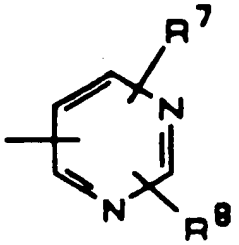
worin R^7, R^8, R^9 jeweils unabhängig voneinander Wasserstoff, ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen, ein Niedrigalkoxy mit bis zu 6 Kohlenstoffatomen, Halogen, vorzugsweise Chlor oder Fluor, bedeutet, oder eine heterocyclische Arylgruppe einer der folgenden Formeln











worin R^7 und R^8 die oben angegebene Bedeutung haben; oder eine Cycloalkylgruppe mit 3-8 Kohlenstoffatomen in der unsubstituierten cyclischen Gruppe; oder eine Adamantylgruppe darstellt;

R^2 Wasserstoff, ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen, ein Niedrigalkoxy mit bis zu 6 Kohlenstoffatomen, oder Halogen darstellt;

R^3 Wasserstoff, ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen, ein Phenylalkyl mit 1-4 Kohlenstoffatomen in der Alkylgruppe oder eine Cycloalkyl-alkyl-gruppe mit 3-8 Kohlenstoffatomen in der cyclischen Gruppe und 1-4 Kohlenstoffatomen in der Alkylgruppe darstellt;

n eine ganze Zahl 0-6 bedeutet;

R^4 Wasserstoff oder ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen darstellt;

R^5 Wasserstoff oder ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen darstellt;

R^6 Wasserstoff, ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen, eine substituierte oder unsubstituierte Arylgruppe, wie für R^1 definiert, darstellt, oder, wenn n 1-6 bedeutet, eine Hydroxylgruppe, oder, wenn n 0 bedeutet, eine Amino-, eine Alkylamino- oder eine Dialkylaminogruppe mit 1-4 Kohlenstoffatomen in den Alkylgruppen darstellt;

A ein Alkylen mit bis zu 6 Kohlenstoffatomen, gegebenenfalls verbunden mit oder unterbrochen durch ein gegebenenfalls substituiertes Heteroatom ausgewählt aus O, S und NR, worin R Wasserstoff, ein Niedrigalkyl mit bis zu 6 Kohlenstoffatomen, ein Phenylalkyl mit 1-4 Kohlenstoffatomen in der Alkyl-

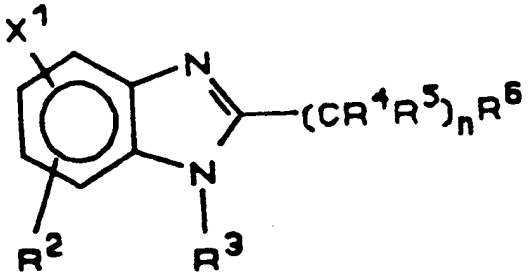
gruppe oder eine Cycloalkyl-alkyl-gruppe mit 3-8 Kohlenstoffatomen in der cyclischen Gruppe und 1-4 Kohlenstoffatomen in der Alkylgruppe; oder ein Alkylen darstellt,
mit der Maßgabe, daß wenn

a) n 0 ist und R^2, R^3 und R^6 alle Wasserstoff bedeuten, die Gruppe A-R^1 nicht 7-Benzylamino oder 7-(4'-Methoxy)-benzylamino ist; und wenn

b) n 1 ist und R^3, R^4 und R^5 alle Wasserstoff bedeuten, R^2 4-Methyl ist und R^6 Ethyl, Phenyl, Benzyl oder (4'-Methoxy)-phenyl bedeutet, die Gruppe A-R^1 nicht 7-Benzyloxy ist; und wenn

c) n 0 ist, R^2 4-Methyl bedeutet, R^3 Wasserstoff bedeutet und R^6 Phenyl darstellt, die Gruppe A-R^1 nicht 7-Benzyloxy ist, durch

A. Umsetzung einer Verbindung der allgemeinen Formel II



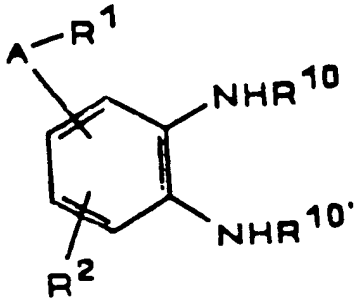
II ,

worin R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben, mit einer Verbindung der Formel III

$R^1(CH_2)_mX^2$ III,

worin R^1 die obige Bedeutung hat, X^1 für -OH, -SH oder -NHR steht und X^2 eine austretende Gruppe ist, wodurch eine Verbindung der allgemeinen Formel I, worin R^1, R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben und m eine ganze Zahl 1-6 ist und A für $-O(CH_2)_m$, $-S(CH_2)_m$ oder $-NR(CH_2)_m$ steht,
erhalten wird;

B. Umsetzung einer Verbindung der allgemeinen Formel IV

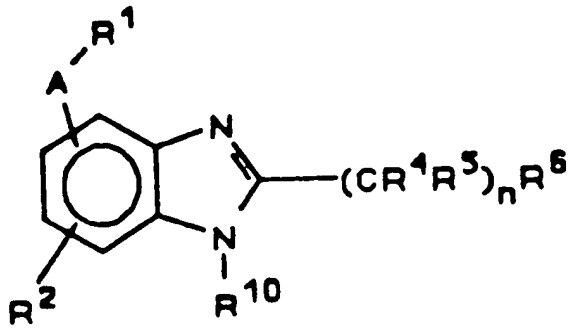


IV ,

worin R^1 und R^2 die obige Bedeutung haben, R^{10} und $R^{10'}$ gleich oder verschieden sind und jeweils Wasserstoff, eine Niedrigalkylgruppe mit bis zu 6 Kohlenstoffatomen oder eine Gruppe oder ein Atom bedeuten, die (das) in eine Niedrigalkylgruppe überführbar ist, mit der Maßgabe, daß wenn eines von R^{10} und $R^{10'}$ eine Niedrigalkylgruppe oder eine Gruppe oder ein Atom, die (das) in eine Niedrigalkylgruppe überführbar ist, bedeutet, das andere von R^{10} und $R^{10'}$ Wasserstoff ist, mit einer Verbindung der allgemeinen Formel V

$R^6(CR^4R^5)_nCOR^{11}$ V,

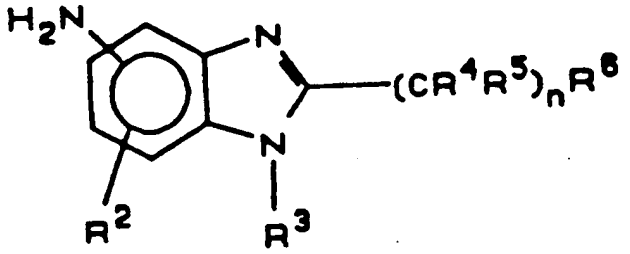
worin R^4, R^5, R^6 und n die obige Bedeutung haben und R^{11} eine austretende Gruppe oder Wasserstoff bedeutet, wodurch eine Verbindung der allgemeinen Formel VI



VI

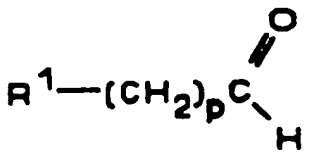
gebildet wird, und nötigenfalls ein Stickstoffatom des Benzimidazolkerns alkyliert und nötigenfalls Schutzgruppen entfernt werden, um eine Verbindung der allgemeinen Formel I zu bilden, und nötigenfalls ein Salz oder Solvat hievon gebildet wird; oder

C. Umsetzung einer Verbindung der allgemeinen Formel VII



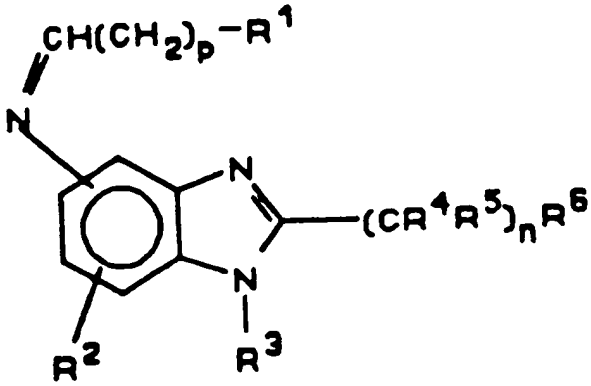
VII ,

worin R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben, mit einer Verbindung der allgemeinen Formel VIII



VIII)

worin R^1 die obige Bedeutung hat und p eine ganze Zahl 0-5 ist, zur Bildung einer Verbindung der allgemeinen Formel IX



IX

worin R^2, R^3, R^4, R^5 und R^6 die obige Bedeutung haben, und nachfolgender Hydrierung der Verbindung der Formel IX zu einer Verbindung der allgemeinen Formel I, worin A für $-NR(CH_2)_m-$ bedeutet und R^1, R^2, R^3, R^4, R^5 und R^6, n und m die obige Bedeutung haben.

2. Verfahren nach Anspruch 1, worin in der Verbindung der allgemeinen Formel I
R^1 die obige Bedeutung hat,
R^2 Wasserstoff, ein Niedrigalkyl mit 1-6 Kohlenstoffatomen, ein Niedrigalkoxy mit 1-6 Kohlenstoffatomen, Chlor, Brom oder Fluor darstellt;
R^3, R^4 und R^5 gleich oder verschieden sind und Wasserstoff oder an Niedrigalkyl mit 1-6 Kohlenstoffatomen darstellen;
R^6 Wasserstoff, ein Niedrigalkyl mit 1-6 Kohlenstoffatomen, eine Hydroxylgruppe oder eine substituierte oder unsubstituierte Arylgruppe, wie oben für R^1 definiert, darstellt, wobei R^1 und R^6 gleich oder verschieden sind;
n eine ganze Zahl 0-6 ist;
A ein Alkylen mit bis zu 6 Kohlenstoffatomen, gegebenenfalls verbunden mit oder unterbrochen durch ein eventuell substituiertes Heteroatom ausgewählt aus O, S und NR, worin R Wasserstoff oder ein Niedrigalkyl mit 1-6 Kohlenstoffatomen ist; oder ein Alkenylen mit bis zu 6 Kohlenstoffatomen darstellt.

3. Verfahren nach Anspruch 1, worin A für $-O-CH_2-$ steht; R^1 Phenyl bedeutet, R^2, R^3, R^4, R^5 und R^6 alle Wasserstoff sind und n 1 ist.

4. Verfahren nach Anspruch 1, worin A für $-O-CH_2-$ steht, R^1 Phenyl bedeutet, R^3 Methyl ist, R^2, R^4, R^5 und R^6 alle Wasserstoff sind und n 1 ist.

5. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine nach einem der Ansprüche 1-4 hergestellte Verbindung enthält.

6. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Verbindung der Formel I oder ein therapeutisch akzeptables Salz hievon zur Hemmung der Magensäuresekretion bei Säugern und dem Menschen verwendet wird.

7. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Verbindung der Formel I oder ein therapeutisch akzeptables Salz hievon als gastrointestinales Zellschutzmittel bei Säugern und dem Menschen verwendet wird..

8. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Verbindung der allgemeinen Formel I oder ein therapeutisch akzeptables Salz hievon bei der Behandlung entzündlicher Erkrankungen des Magendarmtraktes bei Säugern und dem Menschen verwendet wird.

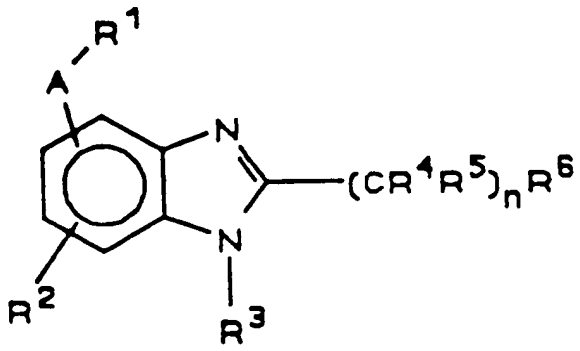
9. Verwendung einer Verbindung der allgemeinen Formel I nach Anspruch 1 ohne die Maßgaben a) - c) bei der Herstellung einer pharmazeutischen Zusammensetzung mit Hemmwirkung auf die Magensäuresekretion.

10. Verwendung einer Verbindung nach Anspruch 9 bei der Herstellung einer pharmazeutischen Zusammensetzung mit entzündungshemmender Wirkung auf entzündliche Erkrankungen des Magendarmtraktes.

Revendications

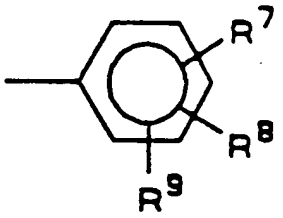
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Composé de formule générale I



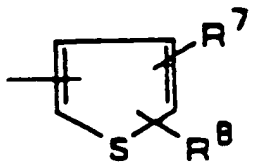
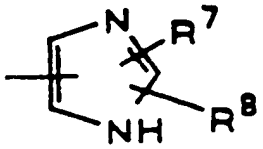
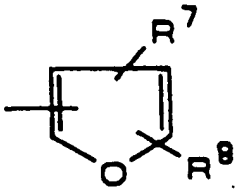
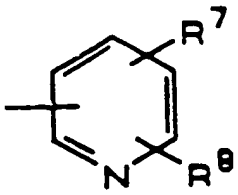
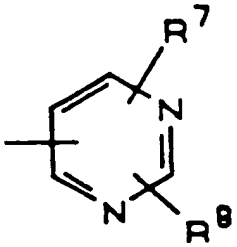
I

ou un sel ou produit de solvatation pharmaceutiquement acceptable, de ce composé, dans lequel :
R^1 représente un groupe aryle substitué, ou non substitué, de formule II'



II'

dans laquelle chacun des symboles R^7, R^8, R^9 représente, indépendamment, un atome d'hydrogène, un groupe alkyle ayant jusqu'à 6 atomes de carbone, un groupe alcoxy ayant jusqu'à 6 atomes de carbone, un atome d'halogène, de préférence un atome de chlore ou de fluor, ou un groupe aryle hétérocyclique répondant à l'une des formules suivantes :

dans lesquelles R^7 et R^8 ont les sens indiqués ci-dessus, ou un groupe cycloalkyle comportant 3 à 8 atomes de carbone dans le groupe cyclique non substitué; ou un groupe adamantyle;

R^2 représente un atome d'hydrogène, un groupe alkyle contenant jusqu'à 6 atomes de carbone, un groupe alcoxy contenant jusqu'à 6 atomes de carbone, ou un atome d'halogène.

R^3 représente un atome d'hydrogène, un groupe alkyle contenant jusqu'à 6 atomes de carbone, un groupe phénylalkyle ayant 1 à 4 atomes de carbone dans le groupe alkyle ou un groupe cycloalkyl-alkyle comportant 3 à 8 atomes de carbone dans le groupe cyclique et 1 à 4 atomes de carbone dans le groupe alkyle;

n est un nombre entier valant 0 à 6;

R^4 représente un atome d'hydrogène ou un groupe alkyle contenant jusqu'à 6 atomes de carbone;

R^5 représente un atome d'hydrogène ou un groupe alkyle contenant jusqu'à 6 atomes de carbone;

R^6 représente un atome d'hydrogène, un groupe alkyle contenant jusqu'à 6 atomes de carbone, un groupe aryle, substitué ou non substitué, tel que défini pour R^1 ou bien, lorsque n vaut 1 à 6, un groupe hydroxyle ou bien, lorsque n est nul, un groupe amino, un groupe alkyl-amino ou un groupe dialkylamino ayant 1 à 4 atomes de carbone dans les groupes alkyles.

A représente un groupe alkylène ayant jusqu'à 6 atomes de carbone et éventuellement relié à, ou interrompu par, un hétéroatome éventuellement substitué, choisi parmi O, S et NR, où R représente un atome d'hydrogène, un groupe alkyle ayant jusqu'à 6 atomes de carbone, un groupe phénylalkyle ayant 1 à 4 atomes de carbone dans le groupe alkyle ou un groupe cycloalkyl-alkyle ayant 3 à 8 atomes de carbone dans le groupe cyclique et 1 à 4 atomes de carbone dans le groupe alkyle; ou un groupe alcénylène ayant jusqu'à 6 atomes de carbone ;

à la condition que , lorsque:

a) n est nul et que les symboles R^2, R^3 et R^6 représentent chacun un atome d'hydrogène , le groupe A-R^1 ne soit pas un groupe 7-benzylamino ou 7-(4'méthoxy)-benzylamino; et lorsque

b) n vaut 1 et que R^3, R^4 et R^5 représentent chacun un atome d'hydrogène, que R^2 représente un groupe 4-méthyle, que R^6 représente un groupe éthyle, phényle, benzyle ou (4'-méthoxy)-phényle, le groupe A-R^1 ne soit pas un groupe 7-benzyloxy; et lorsque

c) n est nul et que R^2 représente un groupe 4-méthyle, que R^3 représente un atome d'hydrogène et que R^6 représente un groupe phényle, le groupe A-R^1 ne soit pas un groupe 7-benzyloxy.

2. Composé de formule générale 1 selon la revendication 1, dans lequel

R^1 est tel que défini ci-dessus,

R^2 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone, un groupe alcoxy ayant 1 à 6 atomes de carbone, un atome de chlore, de brome ou de fluor;

R^3, R^4 et R^5 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone;

R^6 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone, un groupe hydroxyle ou un groupe aryle, substitué ou non substitué selon la définition donnée ci-dessus pour R^1, les symboles pour R^1 et pour R^6 ayant le même sens ou ayant un sens différent,

n est un nombre entier valant 0 à 6;

A représente un groupe alkyleène ayant jusqu'à 6 atomes de carbone, éventuelement relié à, ou interrompu par, un hétéro-atome éventuellement substitué choisi parmi O, S, et NR, où R représente un atome d'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone; ou un groupe alcénylène ayant jusqu'à 6 atomes de carbone .

3. Composé selon la revendication 1, dans lequel A représente -O- CH_2-, R^1 représente un groupe phényle; les symboles R^2, R^3, R^4, R^5 et R^6 représentent chacun un atome d'hydrogène et n vaut 1.

4. Composé la revendication 1, dans lequel A représente -O- CH_2-, R^1 représente un groupe phényle, R^3 représente un groupe méthyle, les symboles R^2, R^4, R^5 et R^6 représentent chacun un atome d'hydrogène, et n vaut 1.

5. Composition pharmaceutique contenant comme ingrédient actif un composé selon l'une quelconque des revendications 1 à 4.

6. Composé défini dans l'une quelconque des revendications 1 à 4, ou un sel thérapeutiquement acceptable de ce composé , destiné à servir à inhiber la sécrétion des acides gastriques chez les mammifères et l'être humain.

7. Composé tel que défini dans l'une quelconque des revendications 1 à 4, ou un sel thérapeutiquement acceptable de ce composé, destiné à servir d'agent cytoprotecteur gastro-intestinal chez les mammifères et l'être humain.

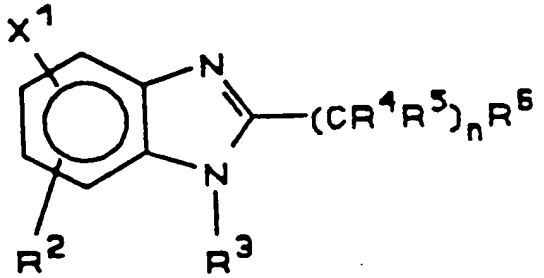
8. Composé tel que défini dans l'une quelconque des revendications 1 à 4, ou un sel thérapeutiquement acceptable de ce composé, destiné à servir au traitement de maladies inflammatoires du tube digestif chez les mammifères et l'être humain.

9. Utilisation d'un composé de formule générale I selon la revendication 1, sans les conditions (a) à (c), pour la préparation d'une composition pharmaceutique ayant un effet d'inhibition de la sécrétion des acides gastriques.

10. Utilisation d'un composé tel que défini à la revendication 9, dans la préparation d'une composition pharmaceutique ayant un effet anti-inflammatoire sur les maladies inflammatoires du tube digestif.

11. Procédé pour la préparation d'un composé de formule I selon la revendication 1, par :

(A) la réaction d'un composé de formule générale (II)



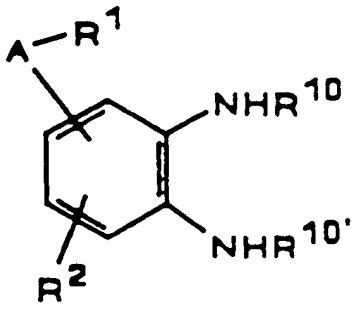
II

[dans laquelle R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus] avec un composé de formule III

$R^1(CH_2)_mX^2$ III

(dans laquelle R^1 est tel que défini ci-dessus; X^1 représente -OH, -SH ou -NHR et X^2 est un groupe partant) ce qui donne un composé de formule générale (I), dans laquelle R^1, R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus et m est un nombre entier valant 1 à 6, et A représente -O$(CH_2)_m$, -S$(CH_2)_m$, ou -NR(CH_2)m;

B) Réaction d'un composé de formule générale (IV)

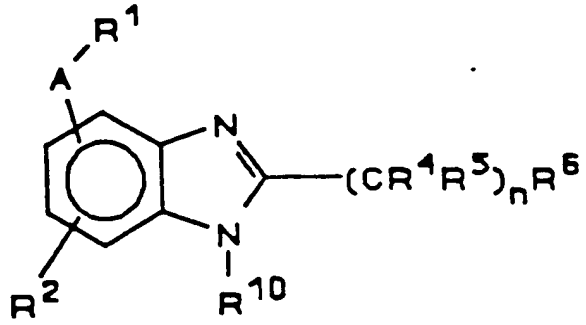


IV

(dans laquelle R^1 et R^2 sont tels que définis ci-dessus; R^{10} et $R^{10'}$ sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle inférieur ayant jusqu'à 6 atomes de carbone ou un groupe ou atome convertible en un groupe alkyle inférieur, à la condition que, lorsque l'un des symboles R^{10} et $R^{10'}$ représente un groupe alkyle inférieur ou un groupe ou atome convertible en un groupe alkyle inférieur, l'autre symbole R^{10} ou $R^{10'}$ représente un atome d'hydrogène) avec un composé de formule générale (V)

$R^6(CR^4R^5)_nCOR^{11}$ V

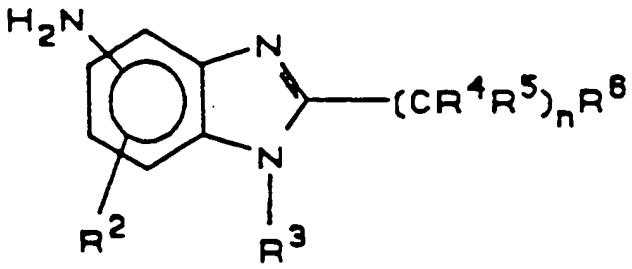
(dans laquelle R^4, R^5, R^6 et n sont tels que définis ci-dessus, et R^{11} est un groupe partant ou un atome d'hydrogène), ce qui provoque la formation d'un composé de formule générale (VI)



VI

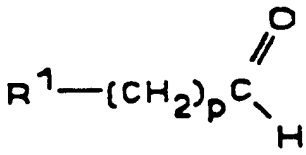
et si nécessaire, on alkyle un atome d'azote du noyau benzimidazole et, si nécessaire, on enlève des groupes protecteurs, pour former un composé de formule générale (I) et, si nécessaire, on forme un sel ou un produit de solvatation de ce composé ; ou

C. Réaction d'un composé de formule générale (VII)



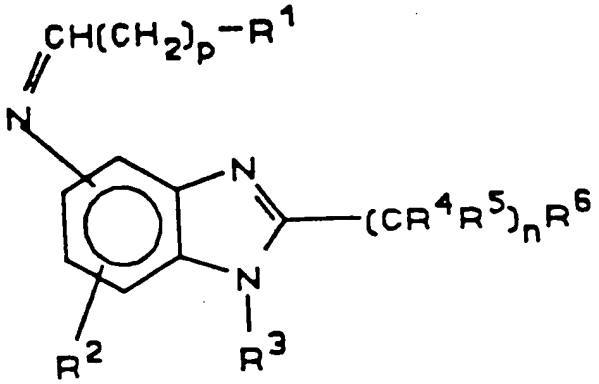
VII

(dans laquelle R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus) avec un composé de formule générale (VIII)



VIII

(dans laquelle R^1 est tel que défini ci-dessus et p est un nombre entier valant 0 à 5) pour former un composé de formule générale (IX)

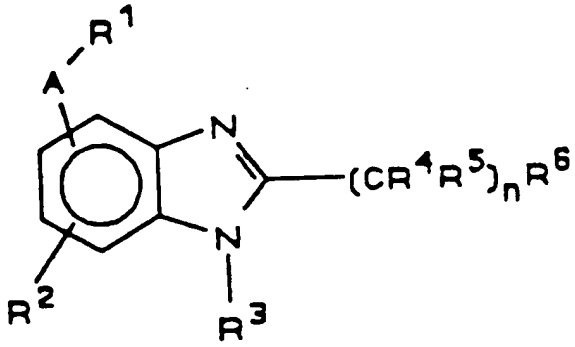


IX

(dans laquelle R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus), puis on hydrogène le composé de formule (IX), ce qui donne un composé de formule générale (I), dans laquelle A représente $-NR(CH_2)_m-$ et R^1, R^2, R^3, R^4, R^5 et R^6 ainsi que n et m sont tels que définis ci-dessus.

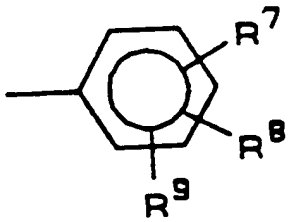
Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la préparation d'un composé de formule générale I



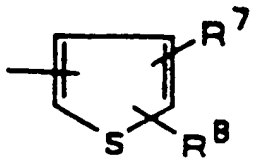
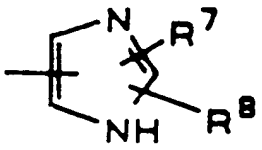
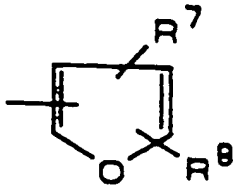
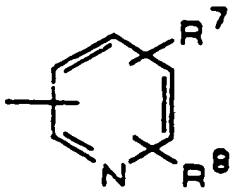
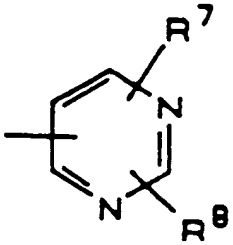
I

ou d'un sel, ou produit de solvatation, pharmaceutiquement acceptables, dans lequel R^1 représente un groupe aryle, substitué ou non substitué, de formule II'



II'

dans laquelle chacun des symboles R^7, R^8, R^9 représente, indépendamment, un atome d'hydrogène, un groupe alkyle inférieur ayant jusqu'à 6 atomes de carbone, un groupe alcoxy inférieur ayant jusqu'à 6 atomes de carbone, un atome d'halogène, de préférence un atome de chlore ou de fluor, ou un groupe aryle hétérocyclique répondant à l'une des formules suivantes

dans lesquelles R^7 et R^8 ont les sens indiqués ci-dessus;

ou un groupe cycloalkyle comportant 3 à 8 atomes de carbone dans le groupe cyclique non substitué; ou un groupe adamantyle;

R^2 représente un atome d'hydrogène, un groupe alkyle inférieur contenant jusqu'à 6 atomes de carbone, un groupe alcoxy inférieur contenant jusqu'à 6 atomes de carbone , ou un atome d'halogène;

R^3 représente un atome d'hydrogène, un groupe alkyle inférieur contenant jusqu'à 6 atomes de carbone, un groupe phénylalkyle ayant 1 à 4 atomes de carbone dans le groupe alkyle ou un groupe cyclo-alkyl-alkyle ayant 3 à 8 atomes de carbone dans le groupe cyclique et 1 à 4 atomes de carbone dans le groupe alkyle;

n est un nombre entier valant 0 à 6;

R^4 représente un atome d'hydrogène ou un groupe alkyle inférieur contenant jusqu'à 6 atomes de carbone;

R^5 représente un atome d'hydrogène ou un groupe alkyle contenant jusqu'à 6 atomes de carbone;

R^6 représente un atome d'hydrogène, un groupe alkyle inférieur contenant jusqu'à 6 atomes de carbone , un groupe aryle, substitué ou non substitué, tel que défini ci-dessus pour R^1 ou bien, lorsque n vaut 1 à 6, un groupe hydroxyle, ou lorsque n est nul, un groupe amino, un groupe alkylamino ou dialkylamino ayant 1 à 4 atomes de carbone dans les groupes alkyles;

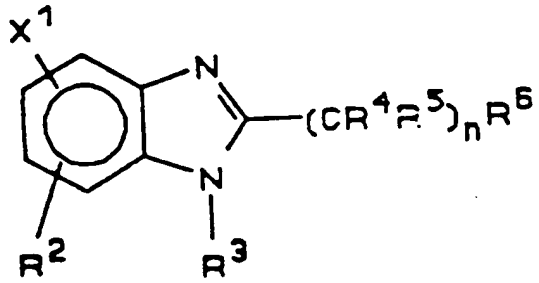
A représente un groupe alkylène, éventuellement relié à, ou interrompu par, un hétéro-atome éventuellement substitué, choisi parmi O, S et NR, où R représente un atome d'hydrogène, un groupe alkyle inférieur contenant jusqu'à 6 atomes de carbone , un groupe phénylalkyle ayant 1 à 4 atomes de carbone dans le groupe alkyle ou un groupe cycloalkyl-alkyle ayant 3 à 8 atomes de carbone dans le groupe cyclique et 1 à 4 atomes de carbone dans le groupe alkyle; ou un groupe alcénylène, à la condition que , lorsque,

(a) n est nul et que les symboles R^2, R^3 et R^5 représentent chacun un atome d'hydrogène, le groupe A-R^1 ne représente pas un groupe 7-benzylamino ou 7-(4'-méthoxybenzylamino; et lorsque

b) n vaut 1 et que R^3, R^4 et R^5 représentent chacun un atome d'hydrogène, que R^2 représente un groupe 4-méthyle, que R^6 représente un groupe éthyle, phényle ou benzyle ou (4'-méthoxy)-phényle, le groupe A-R^1 ne soit pas un groupe 7-benzyloxy; et lorsque

c) n est nul, que R^2 représente un groupe 4-méthyle, que R^3 représente un atome d'hydrogène et R^6 représente un groupe phényle, le groupe A-R^1 ne soit pas un groupe 7-benzyloxy), par

(A) la réaction d'un composé de formule générale (II)



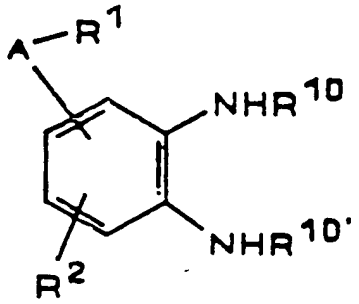
II

[dans laquelle R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus] avec un composé de formule III

$R^1(CH_2)_mX^2$ III

(dans laquelle R^1 est tel que défini ci-dessus; X^1 représente -OH, -SH ou NHR, et X^2 est un groupe partant), ce qui donne un composé de formule générale (I), dans laquelle R^1, R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus et m est un nombre entier valant 1 à 6, et A représente -O $(CH_2)_m$, $-S(CH_2)_m$, ou $-NR(CH_2)_m$;

B) Réaction d'un composé de formule générale (IV)

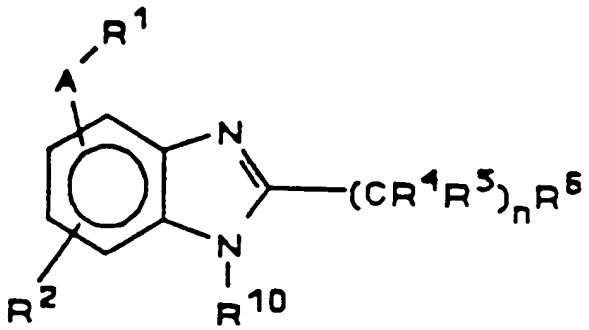


IV

(dans laquelle R^1 et R^2 sont tels que définis ci-dessus; R^{10} et $R^{10'}$ sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle inférieur ayant jusqu'à 6 atomes de carbone ou un groupe ou atome convertible en un groupe alkyle inférieur, à la condition que, lorsque l'un des symboles R^{10} et $R^{10'}$ représente un groupe alkyle inférieur ou un groupe ou atome convertible en un groupe alkyle inférieur, l'autre symbole R^{10} ou $R^{10'}$ représente un atome d'hydrogène) avec un composé de formule générale (V)

$R^6(CR^4R^5)_nCOR^{11}$ V

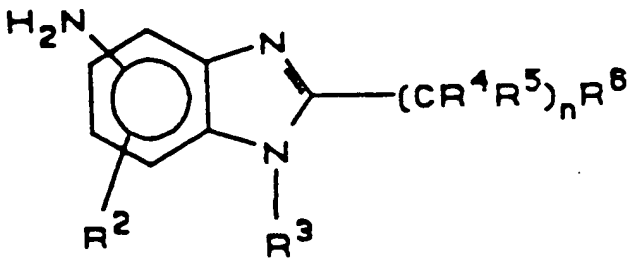
(dans laquelle R^4, R^5, R^6 et n sont tels que définis ci-dessus, et R^{11} est un groupe partant ou un atome d'hydrogène), ce qui provoque la formation d'un composé de formule générale (VI)



VI

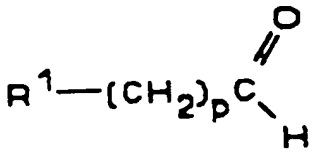
et si nécessaire, on alkyle un atome d'azote du noyau benzimidazole et, si nécessaire, on enlève des groupes protecteurs, pour former un composé de formule générale (I) et, si nécessaire, on forme un sel ou un produit de solvatation de ce composé ; ou

C. Réaction d'un composé de formule générale (VII)



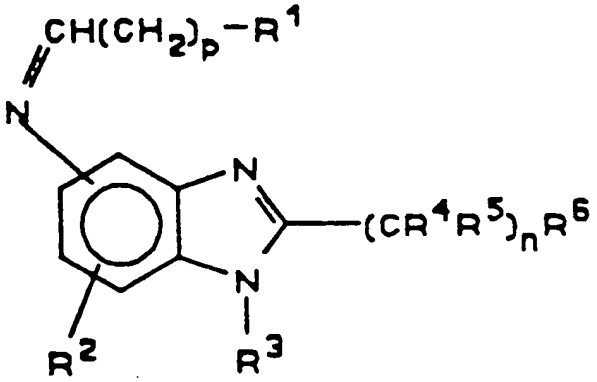
VII

(dans laquelle R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus) avec un composé de formule générale (VIII)



VIII

(dans laquelle R^1 est tel que défini ci-dessus et p est un nombre entier valant 0 à 5) pour former un composé de formule générale (IX)



IX

(dans laquelle R^2, R^3, R^4, R^5 et R^6 sont tels que définis ci-dessus), puis on hydrogène le composé de formule (IX), ce qui donne un composé de formule générale (I), dans laquelle A représente $-NR(CH_2)_m-$ et R^1, R^2, R^3, R^4, R^5 et R^6 ainsi que n et m sont tels que définis ci-dessus.

2. Procédé selon la revendication 1, dans lequel, dans le composé de formule générale (I).

R^1 est défini tel que ci-dessus;

R^2 représente un atome d'hydrogène, un groupe alkyle inférieur ayant 1 à 6 atomes de carbone, un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone, chloro, bromo ou fluoro;

R^3, R^4 et R^5 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 6 atomes de carbone;

R^6 représente un atome d'hydrogène, un groupe alkyle inférieur ayant 1 à 6 atomes de carbone, un groupe hydroxyle ou un groupe aryle, substitué ou non substitué, tel que défini ci-dessus pour R^1, les symboles R^1 et R^6 ayant le même sens ou étant différents ;

n est un nombre entier valant 0 à 6;

A représente un groupe alkylène ayant jusqu'à 6 atomes de carbone, éventuellement relié à, ou interrompu par, un hétéro-atome éventuellement substitué, choisi parmi O, S et NR, le symbole R représentant un atome d'hydrogène ou un groupe alkyle inférieur ayant 1 à 6 atomes de carbone ; ou un groupe alcénylène ayant jusqu'à 6 atomes de carbone .

3. Procédé selon la revendication 1 dans lequel A représente $-O-CH_2-$, R^1 représente un groupe phényle, R^2, R^3, R^4, R^5 et R^6 représentent chacun un atome d'hydrogène et n vaut 1.

4. Procédé selon la revendication 1, dans lequel A représente $-O-CH_2-$, R^1 représente un groupe phényle, R^3 représente un groupe méthyle, R^2, R^4, R^5 et R^6 représentent chacun un atome d'hydrogène et n vaut 1.

5. Procédé pour la préparation d'une composition pharmaceutique caractérisé en ce que la composition contient, à titre d'ingrédient actif, un composé produit selon l'une quelconque des revendications 1 à 4.

6. Procédé selon la revendication 1, caractérisé en ce que le composé de formule (I), ou un sel thérapeutiquement acceptable de ce composé , sert à inhiber la sécrétion des acides gastriques chez les mammifères et les êtres humains.

7. Procédé selon la revendication 1, caractérisé en ce que le composé de formule (I) ou un sel thérapeutiquement acceptable de ce composé, sert d'agent cytoprotecteur du tube digestif chez les mammifères et l'être humain.

8. Procédé selon la revendication 1, caractérisé en ce que le composé de formule générale (I), ou un sel thérapeutiquement acceptable de ce composé, sert au traitement de maladies inflammatoires du tube digestif chez les mammifères et l'être humain.

9. Utilisation d'un composé de formule générale (I) selon la revendication 1, sans les conditions (a) à (c), dans la préparation d'une composition pharmaceutique ayant pour effet d'inhiber la sécrétion des acides gastriques.

10. Utilisation d'un composé , tel que défini à la revendication 9, dans la préparation d'une composition pharmaceutique ayant un effet anti-inflammatoire sur les maladies inflammatoires du tube digestif.